ANNALS OF
INTERNAL MEDICINE

VOLUME 8 NOVEMBER, 1934 NUMBER 5

CLINICO-PATHOLOGIC OBSERVATIONS ON INFANTILE PARALYSIS: REPORT OF 125 ACUTE CASES WITH SPECIAL REFERENCE TO THE THERAPEUTIC USE OF CONVALESCENT AND ADULT BLOOD TRANSFUSIONS: THE POSSIBLE RELATION OF BLOOD GROUP TO THE SEVERITY OF THE DISEASE *

By D. MURRAY COWIE, M.D., F.A.C.P., J. P. PARSONS, M.D., and K. LOWENBERG, M.D., *Ann Arbor, Michigan*

DURING the Michigan infantile paralysis epidemic of 1931 (figure 1) 125 cases came under our observation. Eighty-one of these were first seen in the so-called systemic or pre-paralytic stage, 44 in the paralytic stage. All of the systemic cases received either convalescent poliomyelitis serum, convalescent whole blood, adult whole blood or a combination of these by the various administration routes. Four of these developed paralysis. One was not under our control and is omitted from the total number, leaving 80 treated cases for analysis. Seventy-seven of these, or 96 per cent, did not develop paralysis. In the three patients developing paralysis the involvement was slight, and recovery was complete at the end of one month of convalescence. No case in this series shows any paralysis today.

Of the paralyzed cases, 27 received immunotherapy as soon as they came under observation. Nine of these (33⅓ per cent) showed definite improvement (three completely recovered); 18 cases (66⅔ per cent) showed no improvement (five died). Seventeen paralyzed cases received no immunotherapy; 12 per cent improved, 89 per cent showed marked residual paralysis.

Criteria upon Which the Diagnosis Was Based. Symptoms: Fever, headache, vomiting, diarrhea, constipation, tremor, irritability, drowsiness, sweating, disturbance of breathing and swallowing, dromedary phenomenon. Physical findings: stiff neck, stiff back with or without pain; normal, hyperactive, or lost, tendon cremasteric and abdominal reflexes, spinal fluid

* Presented at the meeting of the American Pediatric Society at Rochester, Minnesota, May 1932.

From the Departments of Pediatrics and Infectious Diseases, and Psychiatry, University Hospital, University of Michigan, Ann Arbor, Michigan.

FIG. 1. Michigan Poliomyelitis Epidemic 1932. Cases reported 1132. Greatest concentration Washtenaw, Wayne (223 cases), Livingston (N.E.), Jackson (N.W.), Ann Arbor center of Washtenaw.

changes (pressure, cell count and cell type, globulin mastic and colloidal gold tests); blood count.

Personnel. All persons connected with this investigation may be considered to have been expert in the work done by them. That is, those examining spinal fluids had had much experience before assisting in the epidemic. The large majority of the counts were made by one man and checked by several others. Those giving intraspinal injections of serum, blood transfusions, and intravenous glucose had also had much experience with this type of work. Blood typing and cross blood typing were done with great care by experienced workers. The physical examinations were carefully conducted and verified. A member of the Department of Anatomy and Orthopedics made complete and almost daily muscle studies on the large majority of the cases, spending practically his entire time at the Contagious Hospital.

Technic in General. The very large majority of treatments were

given in well equipped operating rooms. Most of those patients desiring to remain in their homes were taken to the hospital for their treatments. Those who for some reason could not come to the hospital were cared for at home with scrupulous aseptic technic. A microscope and facilities for blood typing and cross typing were taken to the home.

Coöperation. Perhaps more complete coöperation of the entire citizenry of a community than that shown in our immediate vicinity has never been seen. Anticipating an epidemic of magnitude, a conference was called August 20, and the organization known as the Michigan Commission on Infantile Paralysis was formed. The Commission was financed by the State Medical Society $1,000, the W. K. Kellogg Foundation $4,500, and the Couzens Children's Fund $4,500, making a total of $10,000, the amount estimated necessary to carry out the program. The State was divided into districts, each presided over by a physician chosen by the Commission. Serum was pooled at the State Department of Health and sent to the Commissioners who distributed it free of charge to all indigents and to those who for any reason were unable to pay the otherwise nominal charge. From 460 paid donors, 35,195 c.c. of serum were produced, and 21,530 c.c. were distributed. We are indebted to Dr. C. C. Slemons, State Commissioner of Health, for these figures. The Commission cooperated in every way possible, assisting physicians and defraying expenses for careful medical services. There was no citizen in the State deprived of the best medical care procurable.

Educational campaign lectures were given in the various towns and districts. The press coöperated splendidly in keeping the people informed on how to recognize the disease and how to secure proper service. In our own vicinity, the schools were not opened until the epidemic was well under control. The theaters, churches and Sunday Schools admitted no children. The book stores developed a method of school book purchase and distribution that excluded children from their stores. The press gave daily information on the epidemic urging parents to have their children carefully observed for any manifestation of ill health. Physicians and all people interested in public health were in every way coöperative.

There were naturally many cases observed that were not suggestive of poliomyelitis. On the other hand, we saw many cases with fever, digestive upsets, headaches, etc., which on careful watching did not develop the neck and spine signs, but which may have been abortive forms of the disease. No serum was given to these and no record of them is included in this report.

All the information possible was given the public concerning the high incidence of protection afforded by the immunological treatment as reported by various observers. It seemed to us that there was no one in our immediate community who did not have an intelligent idea of the epidemic. Any fear acquired by this knowledge was legitimate. There was little or no panic. On the other hand, there was a certain confidence

that if the disease was recognized early it could be checked or modified by the use of serum. The difference of opinion concerning the value of serum was kept alive by those who did not favor its use. This apparently had no effect in the response of the public to the advice of the Commission.

Clinical Observations

Group A. Systemic Cases.

Analysis of 80 cases treated during the pre-paralytic or so-called systemic stage of the disease:

Age. The ages varied from 1½ to 45 years: 92½ per cent of the cases were between 1½ and 15 years old.

Fever. All the cases showed fever. The temperatures varied from 101° to as high as 105° F. In 22 per cent it was high, in 32 per cent moderate, in 46 per cent slight. It was moderate or slight in 46 per cent, in which group the three cases of paralysis occurred. The dromedary phenomenon was present in 21, or 26 per cent.

Headache. Headache was complained of in all but four cases. These patients were too young to complain.

Vomiting. Vomiting was present in 43 cases (53 per cent); diarrhea in 12, or 14 per cent; constipation in 26, or 32 per cent.

Tremor. Tremor was observed in 13, or 16 per cent. *Irritability* was noted in 8, or 10 per cent; *drowsiness* in 29, or 36 per cent; *sweating* in 19, or 23 per cent; *neck sign* in 74, or 91 per cent; *spine sign* in 79, or 99 per cent. The *reflexes* were hyperactive in 37, or 45.5 per cent, diminished in 5, or 6 per cent, absent in 7, or 8.5 per cent. The *bulbar type* of the disease was seen in 3 patients, or 3.6 per cent. The *spinal type* in 78, or 96 per cent.

The *spinal fluid cell count* was increased in 78, or 96 per cent. Of the three in which counts were not made, one had otherwise marked manifestations and her sister similarly affected had a spinal fluid cell count of 60. One case, a girl of five years, who was exceptionally irritable, showed marked neck and spine signs, all reflexes hyperactive, headache, vomiting, diarrhea, and fever of 102° F. It was thought best not to do a spinal tap on this patient. The third case, a girl of eight, who had unquestioned manifestations, had a sister with similar manifestations whose spinal fluid showed a cell count of 105.

In 53 cases the spinal fluid cell count was done once. The counts in these cases varied between eight and 1200; in only eight cases was the count below 20. Counts were done twice in 16 cases; they varied between four and 350. In two cases counts of four and eight cells, respectively, were found; in each of these globulin was positive. Counts were done three times in four cases. They were as high as 1200 declining to 150; 950 declining to 19; 90 declining to 6, and 207 declining to 22, respectively.

The *spinal fluid globulin* test was positive in 46 cases, and negative in

28 of the 74 cases in which it was done. In 11 of the latter a check observation was made at a subsequent time. The result was the same. Only once was globulin negative when the mastic test was positive, only twice when the colloidal gold test was positive.

The *spinal fluid mastic* test was done in 39 cases. It was positive in eight, negative in 31. The reaction varied from 011000 to 344222.

Treatment. Twenty-one cases received immunotherapy as early as the second day, 16 the third day, 17 the fourth day, 12 the fifth and sixth days, seven the seventh and eighth days, four the ninth and tenth days, one the thirteenth day and one on the fifteenth day of the disease. Eighty-six and one-half per cent of the cases in this group received treatment between the second and sixth days of the disease. The three cases in which paralysis occurred were treated on the seventh, second and third days of the disease, respectively. One of these received 50 c.c. of convalescent whole blood intramuscularly; one was given a transfusion of 125 c.c. of adult blood, 20 c.c. of convalescent serum in the muscle and 10 c.c. in the spine; and one received a transfusion of 175 c.c. of adult blood and 20 c.c. of convalescent serum in the vein.

In compliance with the request of the Poliomyelitis Commission most of the cases treated outside the hospital received serum intraspinally or intravenously. Only a few of those treated in the hospital were given serum intraspinally. The dose used intraspinally varied between 6 c.c. and 20 c.c., and was given after preliminary removal of a similar amount of spinal fluid. The intravenous dose varied between 10 c.c. and 60 c.c.; the intramuscular dose between 20 c.c. and 50 c.c. Convalescent blood transfusions were given to as many patients as possible. The amount of blood varied between 100 c.c. and 225 c.c. Less than 150 c.c. was given in three cases only; 200 c.c. and over in 11 cases. Adult blood transfusions were given in the same amounts. One patient with bulbar symptoms, was given 325 c.c. of adult blood.

The methods of administration of serum and blood are classified in table 1.

Intravenous glucose, in 20 per cent and 50 per cent solutions, was given in nine cases because of special symptoms, referred to later. The amount varied from 100 c.c. of the 20 per cent solution to as high as 200 c.c. of the 50 per cent solution.

The report of the Michigan Commission on Infantile Paralysis [40] (1931) shows that in a selected group of 233 cases in which *convalescent serum* treatment was given during the pre-paralytic stage, 181, or 76.6 per cent, recovered without developing paralysis, and 52, or 22 per cent, developed paralysis. This is in marked contrast with our series in which 96 per cent recovered without paralysis and 100 per cent developed no permanent palsy. Our series differs in that transfusions of convalescent and adult blood were given in addition to convalescent serum in a large percentage of the cases. This may be responsible for the lower paralysis rate in our series.

TABLE I

Method of Administration of Immunotherapy in the 80 Cases under Complete Control *

	Cases
Convalescent serum alone in the vein	13
" " " in the muscle	5
" " in the vein and spine	9
" " in the muscle and spine	1
" " in the vein and muscle	1
" " in the vein, spine and muscle	3
Convalescent blood transfusion alone	7
" " " and serum in the vein	6
" " " and serum in the muscle	5
" " " and serum in the spine and muscle	1
" " " and serum in the vein and muscle	2
" " " and serum in the spine and vein	1
Adult blood transfusion alone	10
" " " and serum in the vein	8
" " " and serum in the muscle	5
" " " and serum in the spine and muscle	1
" " " and serum in the vein and muscle	1
Convalescent whole blood in the muscle alone	1
	80

* Transfusions were given in 48 cases, 60 per cent.

It is of interest to record the protocols of the paralyzed cases, including the patient who was not under our complete control. They are as follows:

CASE REPORTS

Case 78. Anna W., age 2, was taken ill August 15, 1931, with symptoms suggestive of poliomyelitis. This diagnosis was made before entrance and no details are obtainable. On admission August 21, 1931, six days later, the seventh day of the disease, she did not appear acutely ill. There were none of the usual symptoms except those elicited on physical examination. There were pain and stiffness of the neck and back. The left knee jerk was diminished, the right hyperactive. The spinal fluid cell count was 30, mastic and colloidal gold negative, globulin +++. She was given 50 c.c. of convalescent serum intramuscularly.

On the tenth day (August 25), the cell count was 20, mastic 111000, colloidal gold 0111110000, globulin +++. Between this date and the thirteenth day she developed weakness of the abdominal muscles and paralysis of the left gastrocnemius, dorsal flexors, quadriceps and ham string muscles. She was discharged on the thirty-ninth day, September 28, 1931. There was some residual paralysis of the muscle groups described. This, however, completely cleared up in a short time. We should have transfused this patient. Most of the cases coming in as late or later than this one were given more intensive treatment. On the other hand, there were four cases that received about the same treatment and all of them recovered without the development of paralysis; all had marked symptoms.

Case 79. John D., age 6, was taken ill on August 25, 1931, with severe headache, pain in the neck and back and slight fever. Soon after this he became dizzy and vomited when he sat up. He complained of pain in the temporal region if he raised his arms. The bowels were constipated. Examination was negative except for stiffness of the neck and back and pain in the back on bending forward. The reflexes were hyperactive. He was admitted to the hospital at midnight on this date. The spinal fluid cell count was 1200, mastic negative, colloidal gold 0122100000, globulin negative. He was given 20 c.c. of convalescent serum intramuscularly, and the following morning 10 c.c. intraspinally. Three minutes after this he developed acute abdominal pain, screamed, and tossed about the bed. The pulse became weak. Gen-

eral cyanosis developed and there was a board-like rigidity of the abdomen, spasticity of the lower extremities and marked priapism. Throughout the attack there was excessive thirst. In 45 minutes the attack was over. Soon after this he was given a 125 c.c. adult blood transfusion.

The course of the illness was otherwise uneventful until the day of discharge, the twenty-third day of the disease. At this time it was observed that the gait of his right foot was not quite normal. This became normal in the course of a few days. We are unable to determine the date of the palsy. His muscles were carefully examined almost daily. The day of discharge his cell count was still high, being 110, the globulin ++++, mastic 111000, colloidal gold 1122210000. This patient has no residual palsy.

Case 80. James T., age 5, was taken ill about 6:00 a.m. September 2, 1931, with stiffness of the neck and back, vomiting, severe headache, sweating and constipation. A spinal tap was done. The cell count was 700, globulin ++++. He was given 15 c.c. of convalescent serum in the spine and 45 c.c. in the vein at 5:00 p.m. (second day of disease). We advised giving a blood transfusion and an intravenous glucose injection that night. This was not done. He was brought to the hospital the following morning at 10:00 a.m. (third day). Orders had been left at the ward to give 50 c.c. of 50 per cent glucose and a blood transfusion on entrance. This was not done. A neurologic consultant felt that poliomyelitis was not present; and active treatment was not carried out. The patient seemed to be fairly well during the day, but toward night difficulty in swallowing developed. The following morning (fourth day) when we first saw him these symptoms were exaggerated and there was general cyanosis from bulbar involvement. Fifty c.c. of 50 per cent glucose were given intravenously and he was put in the respirator. He died within a few hours. The autopsy record is presented later.

Because stiffness of the neck and back were the earliest signs observed, it is not at all improbable that there had been symptoms previous to this time (dromedary phenomenon) and that the treatment was given later than recorded above. A brother of this child had been ill a week previously with suspicious signs of poliomyelitis, i.e., headache, disinclination to play, and some pain in the neck. The symptoms, however, were ephemeral. The father, a physician, had been taking care of poliomyelitis cases. A purely neurological opinion during the early stage of the disease is of little or no value. If reliance is placed on it, it may be definitely harmful.

This case is omitted from the series of 81 because it was not completely under our control. We cannot say that this patient would have lived had the prescribed treatment been carried out. Two other cases showing bulbar symptoms lived. They were more intensely treated. One of these, number 12, is of special interest (page 529), and is recorded later.

Case 81. Grace C., age 7, was taken ill October 4, 1931, with sore throat and fever, which cleared up the following day. Fifteen hours before admission to the hospital on October 7, the third day of the disease, the temperature rose again. The patient became very restless and irritable. Later she became drowsy and complained of headache and pain in the right side of the body, particularly in the right leg. When the leg was extended she would cry out. There was no stiffness of the neck but the spine was stiff. The reflexes were all hyperactive. A spinal tap showed 4 cells; globulin, mastic and colloidal gold tests were negative. She was given 20 c.c. of convalescent serum in the vein on entrance and six hours later a transfusion of 175 c.c. of adult blood.

On the fourth day, October 8, careful examination showed extreme muscle tenderness and some weakness of the quadriceps on the right side. On October 13, the ninth day of the disease, reëxamination showed no muscle tenderness, palsy or weakness. In this case the serum was given early. The spinal fluid was negative but the symptoms were marked.

Group B. Paralyzed Cases Treated after Paralysis Developed.

There are 27 paralyzed cases that were given immunotherapy as soon as possible after entrance. These are summarized in table 3. They are grouped together with special reference to the day of the palsy on which they were treated. *Ten were treated on the first day;* of these two completely recovered, two showed definite improvement with only slight residual palsy, four showed no recovery and two, both bulbar cases, died. *Four were treated on the second day;* of these two definitely improved, showing only slight residual palsy; the other two, marked cases, showed no improvement. *Four were treated on the fourth to the fifth day* of the palsy; one of these completely recovered, one, a bulbar case, showed marked improvement with only a slight residual facial palsy, one showed definite improvement and one showed no improvement. *One case treated on the seventh day* was not benefited. Of the remaining eight cases, treated between the thirteenth and the twenty-ninth days of the paralysis, two bulbar cases died, the others showed no improvement.

Of this entire group, three completely recovered. They were treated on the first to the third day of the palsy. Six were definitely improved. This makes a total of nine cases, definitely improved (33⅓ per cent).

Group C. Paralyzed Cases Not Treated.

There were 17 paralyzed cases that did not receive serum. Two improved (12 per cent). Fifteen (88 per cent) showed marked residual paralysis with little or no recovery after entering the hospital. The ages in this group vary from two to 48 years.

If we compare the paralyzed cases that were treated not later than the fifteenth day of the disease with those not treated at all, thus bringing them into line with a similar division treated in the systemic stage of the disease, we have the following results:

Table II

23 Treated Paralyzed Cases		9 Untreated Paralyzed Cases	
Improved	64.3%	Improved	28.5%
Not improved	33.7%	Not improved	71.5%

Intravenous glucose was used in 20 and 50 per cent solutions in 15 cases for relief of headache, pain, muscle tenderness and particularly for bulbar symptoms. The following case we think illustrates benefit from its use:

CASE REPORT

Case 12. Nelson U., age 8, was taken ill on October 2, 1931. He returned home from school in the afternoon with a severe headache. He had complained of being ill during school hours. He then vomited, complained of pain in the back and neck, and of increasing headache. We saw him at 5:00 p.m. We regarded the case as an ordinary case of poliomyelitis. There was characteristic stiffness of the back and neck and the reflexes were hyperactive. At 7:00 p.m. the clinical picture had changed. The temperature had reached 103°. He was stuporous. A spinal tap showed 35 cells, globulin ++++. He was given 6 c.c. of convalescent serum into the spine and 30 c.c. in the vein. He continued to grow worse, the stupor increased, and he became wildly delirious. At times he screamed out with pain apparently in his head. At this time, 10:00 p.m., we gave 75 c.c. of 50 per cent glucose in the vein. Soon after this his delirium was less, he stopped screaming and became quiet. He seemed to fall into a natural sleep but the breathing was not normal. It became very rapid, reaching 60. In a few minutes it became slow, irregular and difficult. There was also difficulty in swallowing. Three hours later, 1:00 a.m., October 3, we gave him 150 c.c. of convalescent whole blood in the vein. Within an hour the situation seemed improved but the breathing difficulty still gave us concern. Two hours later generalized convulsions, rigidity and opisthotonos developed. Ten minims of adrenalin were given at this time for fear that allergy might be playing a part in the reaction. This was followed in a few minutes by 50 c.c. of 50 per cent glucose. The patient relaxed for a while but in a very short time relapsed into convulsions and became cyanotic. We brought him to the Contagious Hospital at this time. His temperature was 104° F., pulse 140, respirations 40. He was given 50 c.c. of 50 per cent glucose in the vein, 1/8 gr. morphine and 1/200 gr. atropine sulphate. The convulsions ceased in an hour's time, and at 8:00 a.m. he was rational. He made an uneventful recovery.

It is our impression that the intravenous glucose (87 grams) was largely responsible for the beneficial results in this case which showed marked manifestations of bulbar involvement. One must also consider the osmotic pull of the blood transfusion as an auxiliary to the glucose. The serum was given early. It did not prevent the occurrence of severe bulbar symptoms. Bulbar manifestations were present at the time the convalescent blood transfusion was given.

We had two quite severe reactions following the use of intraspinal serum. The one just recorded, and case 79. In all, 26 cases received serum by this route. The subject is discussed later.

The Possible Relation of Blood Group to the Severity of the Disease. We have records of the blood type or group in 22 pre-paralytic cases and in 19 paralytic cases. The Moss numerical system of notation is employed in the University Hospital (Groups I, II, III, IV), corresponding to the O, B, A, and AB groups, respectively. Of 130 donors, mostly University students, 2.7 per cent fell in Group I, 35.8 per cent in Group II, 10.5 per cent in Group III, and 51 per cent in Group IV.

Of the 22 pre-paralytic cases, there were 11, or 50 per cent, in Group IV (AB); six, or 27 per cent, in Group III (A); four, or 18 per cent, in Group II (B); and one, or 4.5 per cent, in Group I (O).

Of the 19 paralytic cases there were five, or 26 per cent, in Group IV (AB); three, or 15.7 per cent, in Group III (A); 10, or 52 per cent, in Group II (B); and one, or 5.26 per cent, in Group I (O).

It is of interest, even though the number of cases is small, to note that of the mild or pre-paralytic cases by far the greatest number fall in Group IV, and 77 per cent of them in the combined Groups IV and III, while of the severe or paralyzed cases by far the greatest number fall in Groups I and II (57 per cent). Setting these figures side by side the comparison is better seen.

Mild poliomyelitis, pre-paralytic—77 per cent, Groups IV and III

Severe poliomyelitis, paralytic—57 per cent, Groups II and I

While we have no right to come to a definite conclusion, it is suggestive from these observations that blood Groups IV and III are the most favorable groups and that blood Groups II and I are the most unfavorable; that is, an individual having a Group II or Group I blood may be more likely to have a severe poliomyelitis than an individual with a Group IV or Group III blood.

Our attention is called to the interesting observations of Jungeblut [39] on blood group neutralizing power in poliomyelitis cases. Our results seem at variance with his. Further observations in progress may throw more light on this subject.

Pathological Observations

Acute Cases

Case 80. (James T.) We were able to secure only a small section of tissue from the thoracic cord in this case of marked bulbar poliomyelitis, the clinical history of which has been given earlier.

The gray substance was completely destroyed, containing but a few scattered ganglia cell remains. The nervous tissue was flooded by Hortega elements, astrocytes, lymphocytes and occasional plasma cells, but no leukocytes were present. (Figure 1.) Countless neuronophagias indicated graves of parenchyma elements. Small foci of necrosis were frequent. The blood vessel system was greatly involved and there were numerous small inflammatory foci in the white matter. There was a pronounced acute meningitis.

Case 86. Virgil P., a seven year old boy, came to the Hospital on what was considered to be the third day of the disease. Inquiry leads us to believe that the dromedary phenomenon was present in this case as there was evidence of indefinite symptoms several days previously. On admittance there was moderate fever, drowsiness, breathing and swallowing difficulty, absence of right biceps reflex and a spinal fluid cell count of 2,300. The diagnosis of bulbar poliomyelitis was made. The patient received 150 c.c. adult blood and 300 c.c. 50 per cent glucose intravenously. He died on the first day in the Hospital.

Brain: The leptomeninges are thin and smooth but their blood vessels are enormously dilated and injected. The leptomeninges are bright red in color. Basal vessels are delicate. On frontal sections gray matter is of normal width, of a bluish pink color and the vessels are injected. White matter contains numerous blood points (hyperemia). It is slightly pinkish. The basal ganglia are distinctly outlined and of the same color and appearance as the gray matter. There is a particularly distinct injection of the blood vessels in the medial nuclei of both thalami. A similar condition can be seen in the substantia nigra. All gray nuclei of the subthalamic region, pons and medulla are of a pinkish color, their vessels being dilated and injected. The ventricles are narrow and the ependyma is smooth. There is a small hemorrhage in the pons near the floor of the fourth ventricle.

The leptomeninges of the spinal cord are of the same appearance as those of the cerebrum. The gray matter of the entire cord is very well outlined and distinctly red in color. The white matter is hyperemic.

Spinal Cord: The leptomeninges contain numerous lymphocytes and occasional leukocytes and are somewhat edematous. The inflammation affects the perivascular spaces of the blood vessels of the white matter. The infiltration can be followed up to the gray matter. The white matter itself is edematous and contains fairly numerous foci of proliferated astrocytes and occasional lymphocytes. (Figure 2.)

In the gray matter the anterior horns are severely affected; numerous ganglia elements are destroyed by neuronophagia and the remaining ones show different acute toxic changes. The gray matter is flooded with countless Hortega elements and

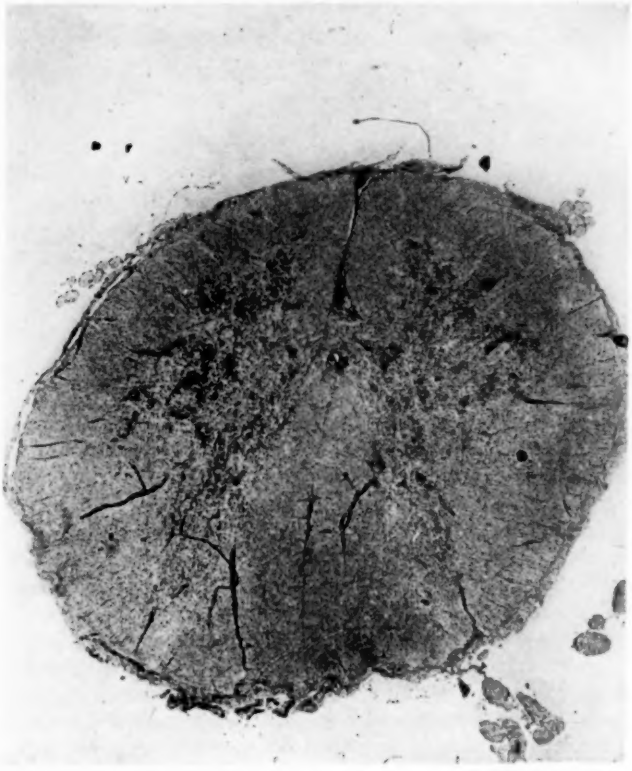


FIG. 2. Multiple neuronophagia in both anterior and lateral horns. Parenchyma entirely destroyed. Blood vessels surrounded by dense infiltrates. Marked infiltration of the meninges in the fissura mediana. Microphotograph × 10. Nissl stain.

astrocytes and the blood vessels are surrounded by dense infiltrates. (Figures 2 and 3.)

The inflammation extends also over the posterior and lateral horns in many areas so that the entire gray matter appears to be transformed into a single inflammatory focus.

The affection is not always symmetrical, the one side being frequently less affected than the other.

The distribution of the disease process in the different segments of the spinal cord varies considerably, the thoracic and cervical regions being more severely affected

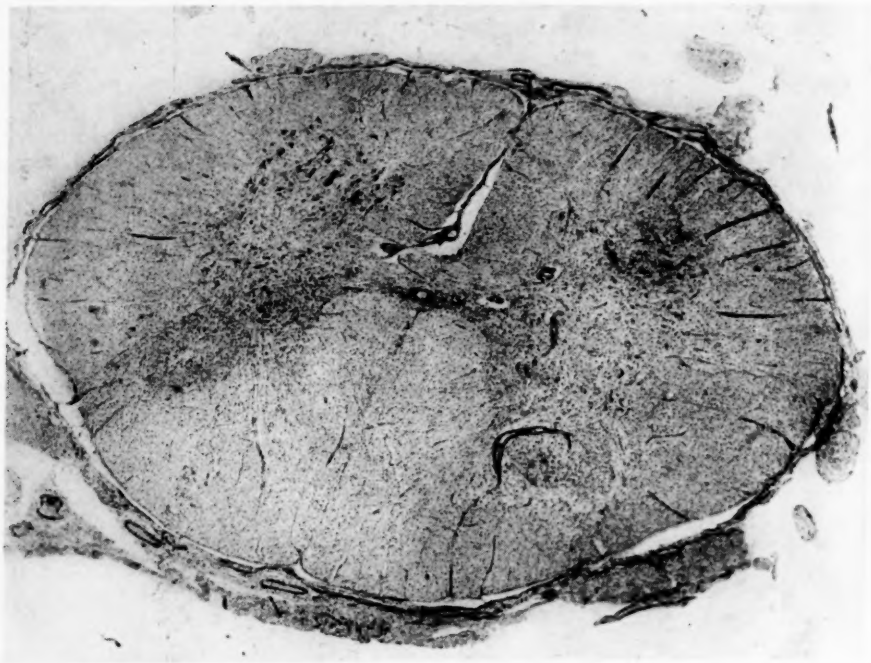


FIG. 3. Multiple neuronophagia in the left anterior horn. Right anterior horn better preserved. Pronounced meningitis and perivascular infiltration in the white matter. Microphotograph × 10. Nissl stain.

than the lumbar. In no segment was the gray matter affected in its continuity and the character of the inflammation was a spotty one.

Medulla and Brain Stem: The affection of the medulla and of the brain stem was studied in sections cut through certain gray nuclei.

At the level of the pyramidal decussation, the histological picture was the same as that observed in different segments of the spinal cord.

On section through the midpart of the olives numerous gray nuclei were found to be affected. Particularly severe was the inflammation in the respiratory area (substantia reticularis); but various other nuclei especially those of the cranial nerves (at this level, nucleus nervi hypoglossi and nucleus ambiguus vagi) were also affected.

The nucleus olivaris inferior remained free: its parenchyma was well preserved. There was no glia activity but a few blood vessels of this nucleus were surrounded by lymphocytic infiltrations. The same condition prevailed in the nucleus olivaris accessorius, medialis and dorsalis.

On the level of the entry of the acoustic nerve a similar picture prevailed. There were numerous inflammatory foci in the corpus restiformis; the substantia reticularis and nucleus nervi vestibularis were uniformly involved; the olives again remained free.

Higher up the nuclei nervi facialis and nervi abducens were both affected. The substantia reticularis represented a very active area of inflammation, but the nuclei pontis were altogether spared.

On section through the nucleus nervi trigemini the floor of the fourth ventricle contained countless inflammatory foci, the peak of the inflammation being in the nucleus of this nerve and in the substantia reticularis.

The inflammation could be traced through the entire central gray substance surrounding the aqueduct and in the lateral fields of the substantia reticularis.

The intensity of the inflammation subsided somewhat in the lower parts of the corpora quadrigemina, the nucleus nervi trochlearis and the stratum griseum centralis being moderately affected.

In the region of the roots of the nervi oculomotorii inflammatory phenomena were seen in a number of formations: in the nucleus of this nerve, in the substantia nigra, in the red nuclei, and in the central gray substance. The intensity of the inflammation was moderate.

The corpora geniculata lateralia were entirely free at this level but the pedunculi cerebri contained numerous infiltrates; a few thrombosed vessels were surrounded by small hemorrhages.

In the hypothalamic region occasional scattered inflammatory foci were present, but the disease flared up again in the thalamus where there were numerous areas of intense inflammation.

The pallidum, putamen and caudate nuclei, the cortex and the entire white substance of both hemispheres were free of pathological changes, but the meninges showed pronounced inflammatory phenomena at the base of the brain as well as over both convexities.

In all regions examined not all gray areas were affected and in those involved the degree of the inflammation varied greatly at different levels. The distribution of the inflammation in the spinal cord and brain stem was not continuous. It was spotty in character, but the histological character was the same throughout.

Case Autopsy Summary

Central Nervous System: The inflammation involves the meninges, the gray matter of the spinal cord and brain hemispheres but spares the white and gray substances of the brain.

The gray substance of the spinal cord, the brain stem, the walls and the floor of the third ventricle and the thalamus are involved in the disease. It cannot be said that the intensity of the inflammation is subsiding in the brain stem, in spite of the fact that certain nuclei of this region were only moderately involved, since it flares up again in the thalamus.

Histologically the disease is characterized by the digestion of parenchyma elements by neuronophagia, intense glia response with formation of astrocytes and Hortega elements and severe generalized involvement of the blood vessel system which is surrounded by dense masses of lymphocytes.

Thymus: Large; measures 11 by 6 by 2 cm. It consists wholly of lymphoid tissue with the thoracic and cervical lobes well represented. Marked hyperplasia of cortex and medulla. Congestion. Extensive hemorrhage into capsule. *Bronchial Glands:* Moderately hyperplastic and show moderate anthracosis. *Cervical Lymph Nodes:* Not examined. *Spleen:* Measures 10 by 5½ by 2½ cm. Weighs 250 grams. Capsule is rather lax and slightly wrinkled. Section shows abundant lymphoid tissue. Cut surface is red in color. The follicles can be seen with the naked eye. No tubercles. Acute passive congestion. Moderate lymphoid hyperplasia. Lymphoid exhaustion. *Large Intestine:* Lymphoid follicles rather prominent. No ulceration. *Small Intestine:* Very large and prominent Peyer's patches. No ulceration. No tubercles found in the mucosa. Lymphoid tissue hyperplastic. Congestion. In the lower ileum there is marked catarrh of the mucosa. *Appendix:* Lymphoid hyperplasia. *Mesenteric Lymph Nodes:* Marked hyperplasia. Three mesenteric lymph nodes near the attachment of the mesentery are almost completely replaced by calcified necrotic material. Congestion. Lymphoid hyperplasia. *Left Adrenal:* Marked hypoplasia of cortex and medulla. Right same. (C. V. Weller.)

Pathological Diagnosis: Acute polioencephalitis. Asphyxiative death. Petechial hemorrhages beneath epicardium, in the thymic capsule and in the gastric mucosa. Pulmonary atelectasis and emphysema. Acute purulent bronchitis and early bronchopneumonia. Acute passive congestion of all organs. Subendocardial fatty degenerative infiltration. Thymico-lymphatic constitution (hyperplastic thymus, generalized lymphoid hyperplasia with lymphoid exhaustion, hypoplasia of adrenals and aorta).

In the summary of the general pathology in this and succeeding autopsy records, detailed data of the lymphatic and lymphoid structures only are given. Somewhat recently attention has been focused on these structures. It should be noted here and will be discussed later that these findings form a familiar picture of the status thymico-lymphaticus.

Case 90. Thomas M., 14 year old boy, entered the hospital on the fourth day of the disease and the first day of the palsy. His symptoms were moderate fever, headache, vomiting, drowsiness, marked neck signs, positive spine sign, normal knee jerks, hyperactive right biceps reflex. The spinal fluid showed 99 cells; globulin three plus; mastic 211000; gold 0122100000. There was marked breathing and swallowing difficulty. Diagnosis, bulbar type of poliomyelitis. Blood Group IV. Thirty c.c. of convalescent serum were given intramuscularly and a transfusion of 250 c.c. of convalescent blood, and 200 c.c. of 50 per cent glucose at a subsequent time. There was no abatement of the symptoms.

AUTOPSY

Brain: The leptomeninges are thin, bright red in color, with strongly injected vessels. The convolutions are somewhat flattened out and the consistency of the brain is firm. The basal vessels are delicate. At the base of both temporal lobes, but especially pronounced on the left side, there is an accumulation of opaque patches resembling somewhat tuberculous lesions. The infundibular region and the pons are free from these changes.

On frontal sections the gray matter is of normal width, pinkish bluish gray in color, with injected blood vessels. It is very distinctly outlined. The white matter is hyperemic but otherwise without gross changes. The basal ganglia are well outlined and of the same appearance as the gray matter. The ventricles are narrow. The thalamus, subthalamic region, floor of the fourth ventricle and gray nuclei of pons are highly hyperemic. The gray matter of all these regions is distinctly pinkish in color.

Spinal Cord: The gray matter of the spinal cord is distinctly pinkish and because of this it is very well outlined. There is considerable edema of the white matter of the spinal cord. Its meninges are bright red and their vessels are injected.

The histological findings in the meninges and the spinal cord were essentially the same as those of case 86. (Potter.)

Medulla and Brain Stem: The inflammation involved the medulla with unusual intensity. The entire floor of the fourth ventricle was transformed into a large and continuous area of inflammation which rendered the differentiation of the single nuclei impossible. The parenchyma was gravely affected and the tissue was flooded by countless neuronophagias, Hortega elements and astrocytes mingled with lymphocytes and leukocytes which migrated into the nervous tissue from the greatly irritated blood vessels. (Figure 4.)

The inferior olives remained essentially free, their parenchyma being well preserved. The intensity of the disease subsided somewhat in the region of the lower corpora quadrigemina but the central gray substance contained numerous inflammatory foci.

At the level of the nucleus of the nervus oculomotorius the inflammation was still very distinct in the nucleus of this nerve, but the substantia nigra and the red nuclei were but moderately involved.

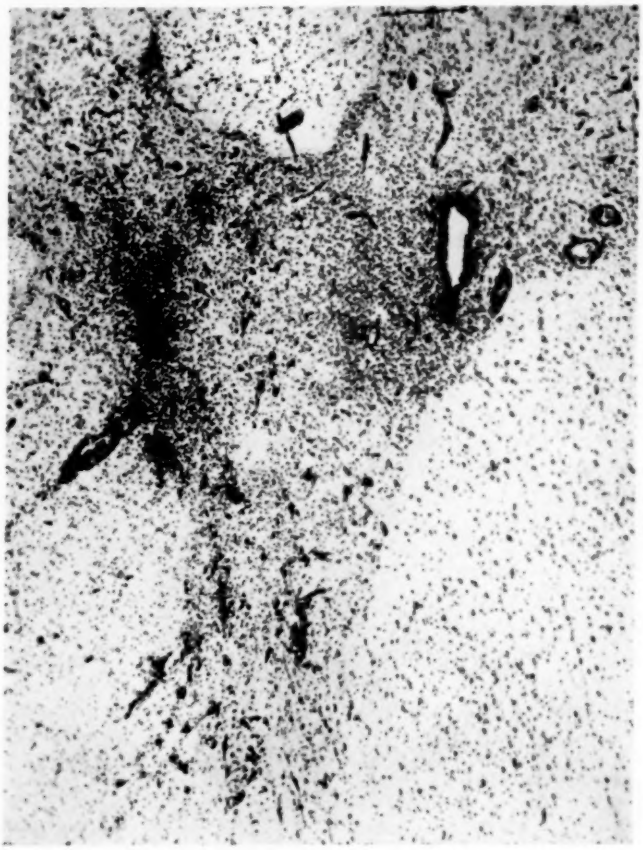


FIG. 4. Anterior horn with scars. Destruction of the parenchyma. Multiple neuronophagia, pronounced glia response. Lateral and posterior horns severely involved. Microphotograph × 40. Nissl stain.

The inflammation could be continuously traced along the aqueduct and numerous foci were seen in the entire hypothalamic region and the thalamus. The pallidum, putamen, caudate nuclei, the white substance of the hemispheres and the cortex were free from pathological changes, but there was an outspoken acute meningitis at the base of the brain.

CASE AUTOPSY SUMMARY

Central Nervous System: The histological picture in this case is characterized by a particularly severe affection of the medulla and brain stem including the hypothalamic region. The sympathetic nervous system is here involved practically throughout.

Thymus: Persistent and hyperplastic, about one-third larger than normal for age and size. *Bronchial Glands:* Small and black on sectioning. *Cervical Lymph Nodes:* Not palpable. *Spleen:* Measures 10 by 6½ by 2½ cm. and weighs 100 grams. It is purplish red in color. The cut section shows marked congestion and hyperplasia of the lymphoid follicles. Marked passive congestion. Moderate lymphoid hyperplasia. *Large Intestine:* Shows moderate congestion, few petechial hemorrhages and hyper-

plasia of the solitary lymph follicles. *Small Intestine:* Shows slight congestion and marked hyperplasia of Peyer's patches and solitary lymph follicles. *Mesenteric Lymph Nodes:* Hyperplastic. Chronic hyperplastic lymphadenitis with stasis catarrh. *Peribronchial Lymph Nodes:* Hyperplastic, congested, with slight anthracosis. *Adrenals:* Hyperplasia of both cortex and medulla. *Retroperitoneal Lymph Nodes:* Hyperplastic lymphadenitis. (C. V. Weller.)

Pathological Diagnosis: Acute meningo-encephalo-poliomyelitis of bulbar type. Marked congestion, edema and small hemorrhages in brain substance. Terminal hemorrhagic purulent lobular pneumonia. Pulmonary congestion, edema and emphysema. Subepicardial fatty infiltration. Right-sided cardiac dilatation with relative tricuspid and pulmonary insufficiency. Thymico-lymphatic constitution (hyperplastic thymus, generalized lymphoid hyperplasia, hypoplasia of aorta and adrenals). Passive congestion and parenchymatous degeneration of all organs.

Case 100. Letha S., poliomyelitis, acute. Entered the Hospital on the nineteenth day of the disease. The history reveals the presence of the dromedary phenomenon. The clinical record shows as leading manifestations, slight fever, marked headaches, constipation, marked irritability, psychoneurotic reactions, marked retention of urine, neck and spine signs, loss of knee reflexes. Spinal fluid showed 160 cells; globulin four plus; mastic 223311; gold 0012222100. Paralysis of both lower extremities, and bladder. Died 44 days after the onset of the disease.

Autopsy

Central Nervous System: The leptomeninges are thin and smooth, their blood vessels somewhat injected.

On frontal sections, the gray matter is of normal width and appearance; the white

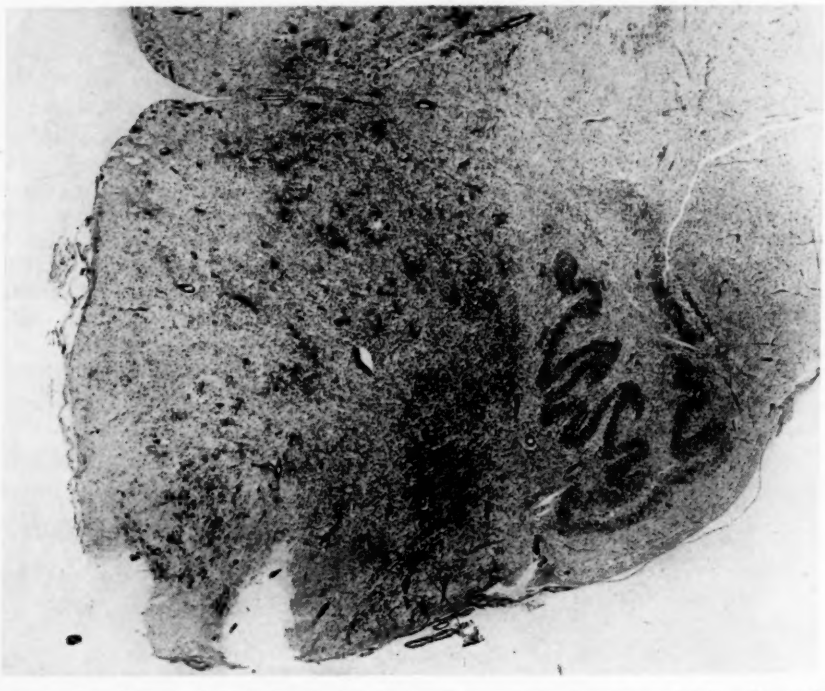


Fig. 5. Multiple foci of inflammation in the floor of the fourth ventricle. Parenchyma of most of the nuclei almost completely destroyed. Olives not affected. Microphotograph × 10. Nissl stain.

matter contains countless blood points. The basal ganglia are well outlined and without gross changes.

The pons is of normal appearance but the medulla shows a pronounced injection of its blood vessels. There is a definite hemorrhagic tinge to the gray matter of the spinal cord and there are small hemorrhages especially pronounced in the thoracic region. The injection of the anterior horns can be followed throughout the spinal cord and increases again in the lumbar region where there are distinct red foci in the anterior horns.

The histological picture of this case differs in many respects from the findings in the two foregoing cases.

In the spinal cord there were countless neuronophagias and severe destruction of

FIG. 6. Massive inflammation of both anterior horns in the lumbar region. Parenchyma completely destroyed. Gray matter flooded with countless glia elements and lymphocytes. Blood vessels surrounded by massive infiltrations. Microphotograph × 10. Nissl stain.

the parenchyma. The infiltrations of the blood vessel system were unusually massive and consisted mainly of lymphocytes mingled with countless plasma elements and polyblasts. Even the finest capillaries were surrounded by these cells which produced histological pictures of unusual intensity. The glia response was in keeping with this. The inflammation was particularly severe in the lumbar portion of the cord and somewhat less pronounced in the thoracic and cervical regions. (Figure 5.)

The meninges were thickly infiltrated by lymphocytes.

In the medulla and brain stem only certain regions were affected. The respiratory area was damaged throughout but the affection was not symmetrical at all levels. There were pronounced inflammatory changes in the nucleus nervi vagi and trigemini.

The substantia nigra presented quite an unusual degree of change. It was affected in the same way and with the same intensity as were the lumbar segments of the spinal cord, and was completely destroyed. (Figure 6.)

The other nuclei of this region, including the substantia grisea centralis, and the hypothalamic region were practically free of changes but there were numerous foci in the thalamus.

In the cortex of both hemispheres, especially in the parietal and temporal lobes, numerous small areas of inflammation were encountered. Their histologic structure was identical with that of the spinal cord lesions.

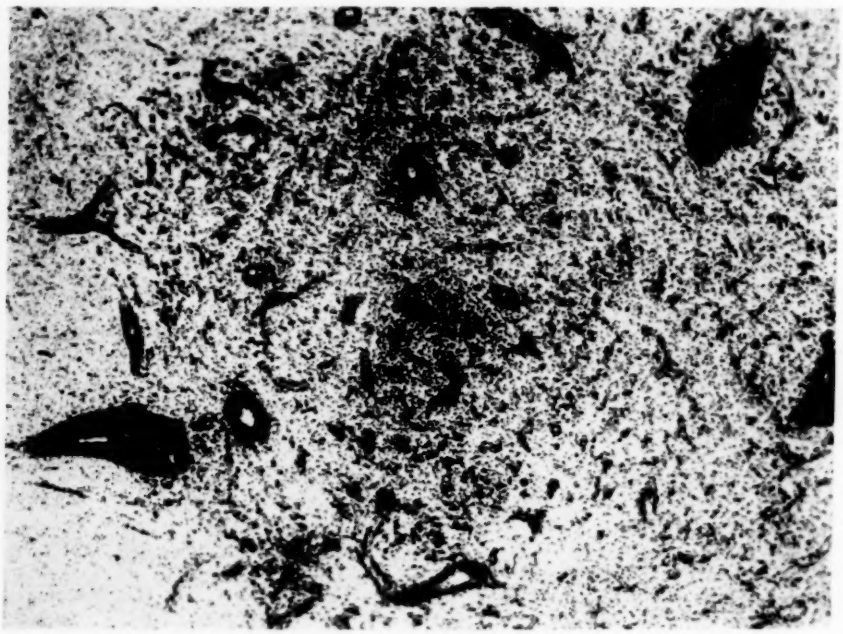


FIG. 7. Massive inflammation of the substantia nigra. Tissue flooded with countless glia elements and lymphocytes. Perivascular spaces contain dense infiltrates (lymphocytes and plasma cells).

CASE AUTOPSY SUMMARY

Central Nervous System: The distribution of the inflammatory lesions is somewhat atypical in this case. The peak of the inflammation is reached in the lumbar cord, again in the substantia nigra and again in the respiratory area. The hypothalamic region is essentially free as are many areas of the sympathetic system; but large areas of the cortex in both hemispheres are affected. The histologic deviation lies in the character of the infiltrating elements which consist largely of plasma elements indicating an intense inflammatory lesion of some duration.

Lymph Glands: Cervicals—no increase in size. *Mesenteric Lymph Nodes:* Not found. *Retroperitoneal Lymph Nodes:* Not made out because of large amount of adipose tissue present. *Hemo-Lymph Nodes:* Not found. *Spleen:* Cut section reveals moderate congestion, and slight increase in the amount of lymphoid tissue. The stroma appears to be somewhat decreased in amount. Atrophy, slight lymphoid exhaustion. Encapsulated tubercles. *Thymus:* Fatty atrophy of a persistent hyperplastic thymus. Small petechial hemorrhages in thymic fat. *Appendix:* Lymphoid hyperplasia of slight degree. Lumen dilated. *Mesenteric Retroperitoneal Lymph Nodes:* Slight lymphoid hyperplasia with sinus catarrh.

Rectum: Contains a small amount of fecal matter. The mucosa near the anal orifice shows three or four shallow ulcers. These are irregular in outline. The

borders are slightly thickened. The floor of these ulcers is smooth and red in color. They are all located within 6 or 8 cm. of the anal orifice. The rectal mucosa higher up is negative except for rather marked congestion. (C. V. Weller.)

Lungs: Pulmonary arteries show recent embolism with induced thrombosis. Emphysema and atelectasis are present. Small atheromatous areas exist in pulmonary artery. Old caseating encapsulated tubercles in the bronchial nodes. Fat stain shows no fat emboli.

Pathological Diagnosis: Acute polio-encephalo-myelitis. Subendocardial fatty degenerative infiltration. Circulatory failure. Parietal thrombosis of right auricular appendage with localized interstitial myocarditis. Pulmonary embolism and induced thrombosis. Subepicardial fatty infiltration. Ulcerative proctitis. Aortic atherosclerosis. Colloid goiter. Lipoidosis of adrenals. Thymico-lymphatic constitution (fatty atrophy of persistent hyperplastic thymus, hypoplasia of aorta and adrenals, slight generalized lymphoid hyperplasia). Old tubercles in bronchial nodes and spleen. Passive congestion, moderate atrophy and parenchymatous degeneration of all organs.

It will be of interest to include the findings of two chronic cases, thus showing the characteristics of permanent changes after the lapse of nine and 30 years, respectively, for the purpose of illustrating our discussion on therapy.

Case 1. A boy of nine years and nine months had contracted poliomyelitis at the age of 13 months.

At *autopsy* the left hemisphere was found to be smaller than the right. The left side of the medulla was atrophic and the cortex of the left hemisphere appeared to be very narrow. Histologic examination showed in the left hemisphere pronounced and widespread degeneration of the parenchyma, numerous areas being almost wiped out. There were no inflammatory changes or tissue response and the blood vessel system was normal. In the atrophic side of the medulla many gray nuclei were destroyed. There were no changes in the cervical part of the spinal cord, the only part of the cord available for study.

Case 2. An entirely different picture was seen in the brain of this case coming to necropsy 30 years after an acute attack of poliomyelitis of the spinal cord. There was a diffuse degeneration and reduction in number of the ganglia cells in the anterior horns where most of the elements were greatly reduced in size and number and deeply stained. The tigroid was still partially visible. Some of these elements were round in shape, others retained the pyramidal form. There were also numerous yellowish weakly stained cells hardly recognizable as parenchymatous elements. Holzer sections revealed considerable glia production in the gray matter. There were no inflammatory phenomena of any kind nor was there any glia response. Weigert preparations failed to show a definite tract degeneration. The medulla and pons were free of changes.

In the substantia nigra a peculiar focal change was seen. The pigmented parenchyma elements were partly destroyed and others were reduced to cell shadows laden with greenish pigment. There were numerous weakly stained greenish nuclear elements, probably also remains of parenchyma. Large astrocytes and proliferated glial nuclei were scattered everywhere. Accumulations of gitter cells were occasionally present in the perivascular spaces. Finally, there were scattered fragments of black or green pigment. Only a small part of the formation was affected.

Examination of the basal ganglia showed that numerous focal lesions the size of a pinhead and somewhat larger, in which the parenchyma was destroyed, were present in the thalami. The gray matter of both parietal lobes also contained numerous old foci. They were organized by glia fibers but otherwise there was no tissue response.

Clinical Comment

It would seem from a study of these carefully observed cases that immunotherapy given in the pre-paralytic stage of acute poliomyelitis must have played a considerable part in bringing about the results obtained. Reference to the spot map of the Michigan epidemic, kindly furnished us by Dr. Slemons, will give the reader an idea of its extent in our immediate neighborhood. Forty-six and one-half per cent of the entire epidemic was concentrated in this vicinity and was contiguous to Washtenaw County, of which Ann Arbor is the county seat. These counties are Wayne (Detroit, the principal city), Oakland, Livingston, Ingham, Jackson, Lenawee, and Monroe. In other words, this was the center of the epidemic.* It is significant that of a group of 80 systemic cases in this area, most of which were intensively treated with convalescent serum and blood transfusions, none is paralyzed today.

There is also some evidence favoring the use of immunotherapy in the early stages of paralysis. It would seem from the progressive nature of the disease that this practice should be encouraged. It was a common observation to see the paralysis extending over a period of days and there are many reports in the literature in confirmation of this characteristic of the disease. Relapses of the disease are well known. One of our autopsied cases demonstrates this unusually well (case 100, page 536). We had regarded this patient as having fully recovered from the acute stage of the disease. It will be recalled that she did not enter our service until the nineteenth day of the illness. She died on the convalescent orthopedic service on the forty-fourth day of the disease. Autopsy disclosed a pulmonary embolus and induced thrombosis, which was thought to be the cause of death. Microscopic examination of the brain showed extensive acute inflammation in the respiratory center, sufficient to cause death.

Because of the widely disseminated vascular involvement which is invariably present, it would seem that this disease peculiarly lends itself to treatment directed at the vascular system either by direct intravenous and arterial measures or indirect intramuscular measures. Everywhere in the meningeal involvement the primary change and almost the entire change is vascular, indicating a breakdown of the meningo-vascular barrier. It would seem that intraspinal treatment might easily produce severe damage to the already widely affected parenchyma. The situation is entirely different from that found in a pure meningitis. The purpose of the therapy should be twofold. First, to neutralize the " toxins " by convalescent serum and blood transfusions, thus protecting the parenchyma from further damage. Second, to relieve edema, thus freeing the nervous tissue from excessive inflammatory response.

We are familiar with the fact that these same pathologic changes may result from infection that does not spread via the vascular system. That

* Number of cases per square mile greater.

is, infection or exciting cause may travel along a nerve trunk, and there is still other evidence which we will present in a subsequent paper, that infection does not necessarily travel via the blood vessels. However, no matter how the infection travels its result is always perivascular infiltration and glia hyperplasia. With this fact in mind it still seems logical to expect that anti-infectious agents must reach these diseased areas via the blood stream.

Physiologists agree that the cerebrospinal fluid is manufactured by the choroid plexuses and passes into the subarachnoid space from the ventricular system. A small amount of the cerebrospinal fluid is delivered to the subarachnoid space via the perivascular spaces that empty into it. In other words, the flow in the perivascular spaces is toward the subarachnoid space. The pressure in the subarachnoid space is greater than the venous pressure. The fluid is absorbed by the subarachnoid villi into the venous sinuses.[38] Substances injected into the spinal canal may be recovered from the veins of the neck in from 30 to 40 seconds, from the stomach and bladder in from 10 to 20 minutes.

Our experience leads us to recommend that 20 to 30 c.c. of convalescent serum in the vein, 20 to 50 c.c. in the muscle, and a transfusion of 100 to 200 c.c. of convalescent or adult whole blood be given, if possible, to all definitely diagnosed systemic cases and to those in the early days of the paralysis. As large doses as possible should be given. From information gleaned from the use of serum in the prevention of experimental poliomyelitis in monkeys a concentrated serum is indicated.

We are impressed with the great benefit that may accrue from the use of intravenous glucose, particularly in the bulbar cases, and also at times in the systemic and spinal paralytic stages. Theoretically, it should be beneficial in the pre-paralytic stage because much damage comes from edema, and because of its effect in improving volume blood flow. We have seen headache, pain, muscle tenderness and circulatory collapse relieved or caused to disappear by its use. Increasing the osmotic pressure of the blood by means of intravenous hypertonic solutions aspirates the cerebrospinal fluid from the shrinking brain tissue causing a reverse flow in the perivascular and ventricular systems.[37]

We are confronted with the request for a satisfactory control for the results we have recorded—for a similarly diagnosed group not treated by immunotherapy. Under the existing circumstances as previously set forth this was impossible.

Perhaps the majority of those who have had much experience with the use of convalescent serum in the treatment of acute poliomyelitis in the pre-paralytic stage are favorably impressed with its action. The favorable literature is quite well known. A few references to it will suffice: Aycock [29] (1927); McEachern and Bell [30] (the Manitoba epidemic, 1928); Shaw, Thelander and Limper [31] (the California epidemic, 1928); Aycock and Luther [32] (a New England epidemic, 1929); Lomer and Shirreff [33] (the

Ottawa epidemic, 1929), a particularly convincing report; and the general review by Amos [34] in 1930.

It would, however, seem particularly important to give heed to all constructively critical reports. We must give particular thought to the mature and exacting judgment of Dr. Park and his associates. Dr. Park [35] remarks, after a careful analysis of a large series of cases: "The results of observations on treated and untreated patients in the pre-paralytic stage of poliomyelitis during the 1931 outbreak (New York) do not give any statistical proof that the serum has any value when given in cases after the cells of the central nervous system are involved. By this involvement we mean the exhibition of the various manifestations of the sympathetic nervous system and the changes in the spinal fluid." Dr. E. L. Godfrey [36] of the New York State Department of Health, discussing Dr. Aycock's paper, questioned the validity of his findings because of the lack of a satisfactory control. We wish to point out the difference in the methods we used in the treatment of our cases, i.e., the addition of blood transfusions.

It may be that the question turns on the pivots of earliness of diagnosis, thoroughness of the education of physicians and public, and the strenuousness of propaganda. The management of the Ottawa epidemic offers one of the best examples of this practice. Without a parallel control and even without a large preëducation campaign series of cases for comparison, one is quite easily convinced of the favorable influence of convalescent serum in that epidemic. The same is true of the Manitoba epidemic. Here a parallel control is recorded. Blood transfusions were not given in these series.

It may be that in a community like Ottawa, information of this nature would be more likely to become the possession of the entire public, to be more widely disseminated and better understood than it would be in a very much larger community made up of a greater number of types and nationalities. If we compare the cases in our small community with those of the much larger community represented by 860 cases selected from the State at large by the Michigan Commission, suggestive figures are obtained. Of the latter, 45.1 per cent became paralyzed, 47.7 per cent were not paralyzed. In our series only 3 per cent were paralyzed and all completely recovered. In his final paragraph, Dr. Park remarks, "Nevertheless, the uniformly optimistic opinions of those who have not observed untreated patients for a comparison cannot be entirely disregarded." We have recorded these cases with the hope that similarly treated series of cases will be reported, particularly with adequate controls, and that our results may be helpful in the final solution of the question as to whether immunotherapy is of value in the treatment of acute epidemic poliomyelitis. We have called attention to the possible relation of blood group to the severity of the disease. Our cases are too few in number to be more than suggestive.

Pathological Comment

We designate the disease process which is characterized by a mesodermal response in conjunction with certain transformations of the neuroglia as encephalitis. This histological symptom complex in encephalitis is a defense reaction in the sense of Aschoff. The histologic criteria in acute poliomyelitis correspond to the following formulations. The mesoderm, that is, the blood vessels of the central nervous system, responds by a production of lymphocytes, polyblasts and plasma cells, and leukocytes are attracted from the blood stream. The glia produces Hortega elements and astrocytes as well as glial nodes. All this is directed against a living virus. *We are therefore dealing with an acute encephalitis.*

The histological picture varies considerably according to the duration of the disease and its acuteness. In stormy cases of short duration considerable numbers of leukocytes may be present. This was noted in case 86. In the majority of the cases, however, it is known that the leukocytes disappear within a few days but that occasionally they may dominate the histologic picture. Luksche [1] described a case of acute poliomyelitis with typical distribution of the disease, in which the infiltrating elements were predominantly leukocytes. In the anterior horn the leukocytes formed themselves in dense masses in the gray matter and occupied the perivascular spaces. Hauptli [2] confirmed the presence of leukocytes in the perivascular spaces as well as in the gray tissue by the oxidase reaction. The same results have been obtained by Wöhrmann.[3] According to Hauptli, the leukocytes are present during the first six days of the disease. This is also in accord with our findings.

The lymphocytes appear at the same time as the leukocytes. They are present during the entire period of acute inflammation. The perivascular infiltrations consist mostly of these cells and they frequently migrate into the gray substance.

The plasma elements for the greater part do not appear in the acute stages. They are more characteristically found in later stages of the disease. They were present in case 100, which terminated fatally 44 days after the onset. They are confined to the perivascular spaces and do not enter the nervous tissue.

The response of the glia and the destruction of the parenchyma is a very impressive finding. A very common type of glia reaction is represented by neuronophagia which is a *phagocytosis* of the *dying ganglia cells* by the proliferating microglia. According to Creutzfeld [4] and others, this neuronophagia is purely a glial response. That is, leukocytes or polyblasts never appear in these foci, never engage in the process of neuronophagia, and the oxidase reaction is therefore always negative.

The neuronophagia, which is almost always present, indicates heavy destruction of the parenchyma. The parenchyma in poliomyelitis is destroyed within a few days. This is an important fact from the standpoint of therapeutic consideration.

Frequent as the neuronophagia may be, it is not uniformly present. It may be missing even in the most acute stages of the disease. In the observation of Wöhrmann [3] neuronophagia was absent in spite of marked parenchyma destruction and acute glia response. Sharp and Nelson [5] had a similar experience.

In very rare instances the glial reaction may be entirely absent, as has been reported by Thomas and Lhermitte.[6] In this case, not even Hortega elements were formed although the ganglia cells were destroyed and the connective tissue response was typical.

The destruction of the parenchyma has naturally attracted great attention and some authors have gone so far as to regard the parenchyma degeneration as independent and preceding the inflammatory phenomena. Recently Hurst [7] again advanced this view, but it cannot be accepted. As mentioned above, poliomyelitis is an acute inflammation of the nervous system and such a condition is never brought about by ganglia cell destruction. Ganglia cell destruction is the result of an inflammation but not its cause. The alteration of the parenchyma constitutes only a part of the inflammation; the ganglia cells suffer in the same way as do the parenchyma elements of other organs under similar conditions.

In certain cases repeated attacks of acute poliomyelitis have been seen; this we observed in case 100, in which there was a relapse before the end of the first attack. Still [8] has reported relapses at intervals of from eight days to 12 weeks. Obviously there occurs in such cases a breakdown of immunity which in poliomyelitis is not always acquired and which is not always a permanent factor. Still describes the case of a child who contracted poliomyelitis at the age of 21 months and suffered a permanent paralysis of the left leg. The second attack at the age of 7½ years left no damage.

Peremans [9] reports the case of a child of four years and nine months, with a second attack three months and a third attack two years after the first one. The child survived. The second attack may be fatal no matter when it occurs, whether a few weeks after the first onset as in our observation (100) or several years later, as in the case of Marinesco and Draganesco.[10] In the latter instance, acute changes of the second attack as well as old scars and parenchyma degeneration of the first were present.

As has been pointed out, the virus of this disease affects the anterior and posterior as well as the lateral columns of the spinal cord, the gray masses of the medulla and pons, of the subthalamic region, and of the wall of the third ventricle. All of these regions contain numerous centers which are a part of the sympathetic nervous system. *Acute poliomyelitis is to a great extent a disease of the sympathetic system.* In the clinical picture even in the acute stages, it will be noted that there are many symptoms which confirm this view, one of the most important features being the disturbance of the respiratory area. The frequency of this type of disturbance is in accord with the frequency of anatomical lesions in this region which was affected in all of our autopsied cases.

According to Léchelle, Baruk and Douady [11] vasomotor and sympathetic disturbances may result from the involvement of the lateral horns characterized by pains of radicular type and vasomotor and sympathetic disturbances in the extremities.

The frequency of the affection of the sympathetic system has been shown by Wernstedt [12] who examined 6775 cases of the great Swedish epidemic of 1911–1913. He reported numerous instances of accommodation, bladder and anal sphincter palsies, as well as those of the lips, tongue and vocal cords.

In other instances the involvement of the sympathetic nervous system is restricted to certain brain stem nuclei. A great deal of attention has been paid to isolated facial palsies frequently occurring in epidemics of poliomyelitis, a number of which were observed in this series. Radovici [13] saw 15 cases and Stern [14] had a similar experience. The isolated affections of the abducens (sixth) and motor oculi (third) nuclei (case 95) (Lundsgaard [15]) as well as those of the vagus (Nemlicher [16]) also belong here. Disturbances of the bladder in the initial stages of the disease have been reported by Bugbee,[17] and observed by us in two cases. All of these localized types of poliomyelitis were acute in character and were frequently fatal. None of our facial cases were fatal. One of our bladder cases died.

In a few instances the affection of the sympathetic nervous system has run a chronic course. Mendel [18] described a peculiar, slowly increasing, bluish discoloration of the left leg in a young male. This extremity became cool and gradually an atrophy of thigh and calf, including the bones, developed. Hypasthesia, hypalgesia and hypothermia were noted. According to Mendel the clinical picture was caused by the involvement of the lateral horns of the spinal cord. Chronic progressive palsies of arms and legs associated with severe muscle atrophies have been seen by Comfort.[19] Particularly severe and remarkable were the disturbances in the observations of Sterling [20] and Foster Kennedy.[21] Sterling described palsies of the legs, of the muscles of the trunk and of the left facial nerve, acute bilateral panophthalmia and slowly progressing atrophy of the face involving its skin, muscles, bones and teeth. The author interprets his findings as a vegetative trophoneurosis. Foster Kennedy saw in a boy of 12 a sudden complete paralysis associated with a loss of bladder and rectal control. In the third week of the disease, lanugo hairs appeared all over the body. The patient recovered but the hair of the head stopped growing for several months.

The pathology of these chronic affections of the sympathetic system is but little known. Two possibilities have to be considered: (1) destruction of certain gray nuclei, and (2) changes in the paravertebral sympathetic trunks, or both.

Histologic changes in the sympathetic ganglia of the trunk and even in those of the intestines have been reported several times, but they are not convincing. Chronic lesions of the brain have been described in the litera-

ture in rare instances. Gross involvement of the brain has been described by Koenig,[22] who reported hemiatrophy of the body and the extremities, which in some instances but not in all was associated with hemiatrophy of one of the hemispheres. We are able to confirm this finding. (See page 539.) The degeneration of the sympathetic nuclei in the medulla has been demonstrated by us in one chronic case. Bouttier and van Bogaert [23] reported diffuse degeneration of the spinal cord including the lateral horns, a finding similar to that described in the cord of our second chronic case.

The number of observations of chronic cases is, however, too small to warrant conclusions; but we have reason to believe that chronic changes of the sympathetic nervous system are more frequent than is generally known. This suggests the importance of investigating the possibility of preventing further development of the disease after the first signs of paralysis have developed. Our observations show that the poliomyelitis may very well produce severe and permanent destruction of the gray matter and that the disease is not always restricted to the spinal cord and the brain stem. The earlier in life the infection takes place the more damage it can do. In an infant with undeveloped and delicate nervous system the disease may interfere with further mental progress and produce idiocy or feeble-mindedness. The course of the disease in an infant is much more severe than it is in an older child.

Clinical, histological and etiological considerations have been used in order to work out a pathologico-anatomical classification. It has proved to be impossible to harmonize them. The etiology of poliomyelitis is not known and the histologic findings are shared by other types of encephalitis. These were the reasons which compelled H. Spatz [24] to propose a new classification based on the modus of the distribution.

Acute poliomyelitis is characterized by the involvement of the gray tissue of the spinal cord and brain stem. It is, therefore, a polioencephalitis and treatment must be directed at wide and scattered areas of infection. The distribution of the inflammation in the affected areas is spotty. This peculiar modus of distribution as well as the histologic response is shared by rabies, epidemic encephalitis, and the so-called Borna disease in horses. They constitute, therefore, one histologic group.

The similarity is limited to the acute forms of these diseases. The chronic conditions present entirely different pictures. Poliomyelitis destroys numerous gray nuclei in the spinal cord, in the medulla, the brain stem, and in wide areas of the gray matter—lesions which are very unusual in epidemic encephalitis. In the latter, only the substantia nigra suffers a permanent degeneration and the resulting histologic picture differs fundamentally from that which we observed in the same region in our second chronic case. Chronic rabies is not known. The four diseases in question are four independent biological units produced by different, although in all instances, ultramicroscopic viruses. Their therapy and their prophylaxis may be found to involve the same principles.

Different views have been advanced for the explanation of the peculiar distribution of the disease in the central nervous system. Spatz is of the opinion that the virus may reach the brain by way of the spinal fluid because the basal parts of the brain and its inner surfaces, as for example the walls of the third and the floor of the fourth ventricle, which are exposed to the spinal fluid, are particularly affected. He thinks that the virus travels through the peripheral nerves and reaches the spinal fluid in this way. This view may seem to be confirmed by experimental transmission of the virus through the ischiatic nerve or the cervical ganglia (Marinesco,[25] Hurst[26]). Such an assumption, we think, is not tenable because typical infection may be produced by intracerebral injection without involving the spinal fluid.

Jungeblut and Spring[27] separated the lower part of the spinal cord in monkeys and closed the dura so that the spinal fluid passage remained free. An intracerebral inoculation produced a typical poliomyelitis in the animal but the infection did not pass the lesion. The virus traveled, therefore, through the nervous tissue itself, and not by way of the spinal fluid. This may lend further support to our feeling that intraspinal serum is unnecessary.

The pathology of the body organs in poliomyelitis is unimportant. The changes in the lymph glands as described by Flexner, Peabody and Draper,[28] 20 years ago, and by us, are characteristic of status thymico-lymphaticus. They are not peculiar to poliomyelitis. Catarrhal inflammation of the intestinal mucosa and of the lymphoid structures is not uncommon in other infectious diseases in childhood. It seems to us that the somewhat revolutionary view of Burrows, who believes that poliomyelitis infects first the lymphatic structures and only secondarily and in rare instances the nervous system, is rather speculative. Cowie and Lowenberg * have noted these general lymphoid changes in experimental poliomyelitis in monkeys inoculated intracerebrally.

From the standpoint of symptomatology, there is abundant evidence of central nervous system involvement in a very large percentage, if not in all, of the cases which do not go on to the stage of paralysis. There seems to be evidence of a systemic stage of this disease prior to involvement of the nervous system, as there also is in epidemic meningitis. This favors the opinion that the virus is probably carried to the central nervous system by way of the blood stream and encourages therapeutic effort via this route, although it is well known that the virus may travel along the nerve sheath, as has been accomplished experimentally. Dr. Flexner's well known experiments on monkeys show that the disease virus may travel through the nose directly along the olfactory nerves; and there is rather convincing evidence that the virus enters the body through the nasal passages in man. We have not been able to demonstrate changes in the olfactory

* Unpublished records.

nerves. We have seen involvement of the cranial nerves after intracerebral injection of poliomyelitis virus in monkeys.

Summary

In the four cases of acute poliomyelitis that came to autopsy, there was an acute inflammation in the spinal cord and brain stem in all and in the gray matter of the brain in one. In one case the spinal cord alone was available for study.

In the spinal cord, anterior, posterior, and lateral horns were affected and the greater part of their parenchyma was destroyed. Neuronophagia was very frequent and the glia response was very active. The blood vessel system of the cord was severely involved.

In the medulla and brain stem numerous gray nuclei were affected in the same way as the gray matter of the spinal cord, the floor of the fourth ventricle being particularly involved. There were numerous foci in the thalamus in two cases. In these the inflammation was spotty, the foci being not always interconnected. The gross pathology invariably showed extensive edema. The progressive nature of the involvement was very apparent.

Two chronic cases were also examined. In one, there were numerous old degenerative foci in the gray matter of the spinal cord, in the substantia nigra, in the thalamus and in the gray matter of the brain. In the other, large areas of the gray matter were destroyed and the medulla was hemiatrophic.

The histologic picture varies in relation to the duration of the disease; it is dominated by the destruction of the parenchyma.

Acute poliomyelitis shows a far-reaching conformity with acute epidemic encephalitis, rabies and Borna's disease of the horse. Poliomyelitis affects the sympathetic system to a great extent. It may cause idiocy if it occurs in infancy.

Conclusions

1. We have recorded a study of 125 cases of epidemic poliomyelitis including data upon which our conclusions are based; 81 in the pre-paralytic stage, 44 in the paralytic stage. The cases developed in the center of the epidemic. There are also recorded a few chronic cases for purpose of discussion.

2. Eighty of the pre-paralytic cases were under our complete control. They received either convalescent serum, convalescent or adult whole blood transfusion, or a combination of these by the various routes of administration. Seventy-seven, or 96 per cent, of these did not develop paralysis. In those developing paralysis, recovery was complete. No case shows any residual paralysis today.

3. Twenty-seven of the paralyzed cases received immunotherapy as soon as they came under observation. Of these 33⅓ per cent showed

definite improvement. Three completely recovered; five died. Seventeen paralyzed cases received no immunotherapy; 11.6 per cent improved, 86.64 per cent showed marked residual paralysis with little or no recovery.

4. The progressive nature of the pathologic involvement of the central nervous system as observed clinically strongly suggests that immunotherapy and osmo-therapy should also be carried on in the early stages of the paralysis.

5. Acute poliomyelitis involves the gray matter of the spinal cord, the nuclei of the brain stem, and the walls of the third ventricle. It is, therefore, mainly an infection of the sympathetic nervous system. The basal ganglia and the cortex are in some instances involved. Scattered foci may be present in the white matter.

6. Histologically the disease is characterized by the involvement of the neurons which are destroyed by the so-called process of neuronophagia.

7. The inflammatory edema which is present in all acute cases must be regarded as an important factor in therapy and must be relieved.

8. Epidemic poliomyelitis is a non-purulent type of inflammation. It is one of a biologic group of diseases comprising rabies, epidemic encephalitis, and Borna's disease of horses.

9. Histologic examination of chronic cases shows that in some instances the infection involves the entire cortex and interferes with the further development of the nervous system, producing feeble-mindedness and idiocy.

10. The importance of the involvement of some of the brain areas, for example, the substantia nigra, is not manifested clinically as is a similar involvement following epidemic encephalitis by the Parkinsonian syndrome.

11. Clinico-pathologic data are given which should assist in determining the results of the therapeutic measures employed.

12. Blood group may be an influencing factor in the severity of the disease. Seventy-seven per cent of the pre-paralytic cases fell in Types IV and III; 58 per cent of the paralyzed cases fell in Types II and I.

We wish to express our sincere appreciation of the devoted assistance during the epidemic of Dr. Dorman E. Lichty and Mr. William Hicks of the Contagious Hospital Staff, Miss G. Kleinheksel, supervising nurse, and Drs. Norman Capener and Louis Yglesias of the Orthopaedic Staff.

BIBLIOGRAPHY

1. Luksche, A.: Ein Fall von Poliomyelitis anterior, Verhandl. deutsch. Arzte Prag. Sitzung von 9.5, 1924.
2. Hauptli, O.: Zur Histologie der Poliocnz. acuta, Deutsch. Ztschr. f. Nervenheilk., 1921, lxxi, 1.
3. Wöhrmann, W.: Über Poliomyelitis anterior acuta, Virchow's Arch. f. path. Anat., 1926, cclix, 466–488.
4. Creutzfeld, H. G.: Zur Histopathologie der experimentellen Poliomyelitis acuta (Heine-Medin) beim Affen und Meerschweinchen, Ztschr. f. Hyg. u. Infektionskrankh., 1925, cv, 402–415.
5. Sharp, R., and Nelson, G. R.: Bulbar type of acute poliomyelitis, Trans. Am. Neur. Assoc., 1922, cciii.

6. THOMAS, A., and LHERMITTE, J.: Les lésions cérébrales et médullaires de la poliomyélite aiguë de l'adulte, Rev. neurol., 1929, i, 1242–1250.
7. HURST, E. W.: Histology of experimental poliomyelitis, Jr. Path. and Bact., 1929, xxxii, 457–477.
8. STILL, G. F.: Second attacks of acute poliomyelitis and minimal duration of immunity, Arch. Dis. Child., 1930, v, 295–298.
9. PEREMANS, G.: Attaques répéteés de paralysie infantile, Scalpel, 1923, lxxxvi, 1319.
10. MARINESCO, G., and DRAGANESCO, S.: Un cas suraigu de la maladie de Heine-Medin, Ann. d'anat. path., 1928, v, 153–155.
11. LÉCHELLE, P., BARUK, H., and DOUADY, D.: Poliomyélite aiguë avec troubles sympathiques intenses ayant simulé une artérite oblitérante, Bull. et mém. Soc. méd. d. hôp. de Paris, 1927, li, 500–503.
12. WERNSTEDT, W.: Klinische Studien über eine zweite grosse Poliomyelitis-Epidemie in Schweden 1911–1913, Ergebn. d. inn. Med. u. Kinderh., 1924, xxv, 705–820.
13. RADOVICI, A.: La paralysie faciale épidémique au cours de l'épidémie actuelle de poliomyélite en Roumanie, Presse méd., 1928, xxxvi, 516.
14. STERN, W.: Poliomyelitis unter dem Bilde isolierter Facialislähmung, Med. Klin., 1926, xxii, 1600.
15. LUNDSGAARD, K. K. K.: Einige Fälle von erworberner Augenmuskellähmung bei Kindern (Poliomyelitis anterior, Heine-Medin-Krankheit), Klin. Monatblt. f. Augenh., 1912, ii, 734–739.
16. NEMLICHER, L.: Zur Charakteristic der Epidemie der Heine-Medin Krankheit in Charkow im Herbst 1924.
17. BUGBEE, H. G.: Paralysis of bladder with acute poliomyelitis, Jr. Urol., 1925, xiii, 333–335.
18. MENDEL, K.: Poliomyelitis chronica lateralis, Neurol. Zentralbl., 1916, xxxv, 694.
19. COMFORT, M. W.: Chronic anterior poliomyelitis with achondroplasia, Med. Clin. N. Am., 1925, viii, 1287–1293.
20. STERLING, W.: Ungewohnliche trophische Storungen bei der Heine-Medin Krankheit, Polska Gaz. Lek., 1928, vii, 44.
21. KENNEDY, F.: A case of acute epidemic poliomyelitis, Jr. Nerv. and Ment. Dis., 1912, xxxix, 558.
22. KOENIG, W.: Über die bei den cerebralen Kinderlähmungen zu beobachtenden Wachsthumsstörungen, Deutsch. Ztschr. f. Nervenh., 1900, xix, 63–86.
23. BOUTTIER, H., and VAN BOGAERT, L.: A propos d'un cas anatomoclinique de poliomyélite infantile, Ann. de méd., 1923, xiv, 89–107.
24. SPATZ, H.: Encephalitis, Handbuch der Geisteskrankheiten Herausgegeben von O. Bumke, Vol. 2, Part 7, page 157.
25. MARINESCO, G.: De la transmission du virus de la Poliomyélite par des nerfs périphériques et ses rapports avec les infections ascendantes, Compt. rend. Soc. de biol., 1911, lxx, 286–288.
26. HURST, E. W.: Further contribution to pathogenesis of experimental poliomyelitis; inoculation into sciatic nerve, Jr. Path. and Bact., 1930, xxxiii, 1133–1143.
27. JUNGEBLUT, C. W., and SPRING, W. J.: Note on propagation of virus in experimental poliomyelitis, Proc. Soc. Exper. Biol. and Med., 1930, xxvii, 1076–1078.
28. FLEXNER, S., PEABODY, F., and DRAPER, G.: Epidemic poliomyelitis; twelfth note: the visceral lesions of human cases, Jr. Am. Med. Assoc., 1912, lviii, 109–111.
29. AYCOCK, W. L., and KAGAN, J. R.: Experimental immunization in poliomyelitis, Jr. Immunol., 1927, xiv, 85; *abstr.* Jr. Am. Med. Assoc., 1927, lxxxix, 1638.
30. MCEACHERN, J. M., and BELL, L. G.: Lessons from poliomyelitis epidemic in Manitoba, 1928, Canad. Public Health Jr., 1929, xx, 427–430.
31. SHAW, E. B., THELANDER, H. E., and LIMPER, M. A.: Treatment of poliomyelitis, Jr. Am. Med. Assoc., 1931, xcvii, 1620–1624.

32. Aycock, W. L., and Luther, E. H.: Preparalytic poliomyelitis, observations in 106 cases in which convalescent serum was used, Jr. Am. Med. Assoc., 1928, xci, 387–394.
33. Lomer, T. A., and Shirreff, W. T.: Report on epidemic of poliomyelitis in Ottawa, 1929, Canad. Med. Assoc. Jr., 1930, xxii, 228–234.
34. Amos, H. L.: Poliomyelitis, Southern Med. Jr., 1930, xxiii, 18–21.
35. Park, W. H.: Therapeutic use of anti-poliomyelitis serum in preparalytic cases of poliomyelitis, Jr. Am. Med. Assoc., 1932, xcix, 1050–1053.
36. Godfrey, E. L.: Jr. Am. Med. Assoc., 1927, lxxxix, 23, 1925.
37. Weed, L. H.: Cerebrospinal fluid, Physiol. Rev., 1922, ii, 171–203.
38. Weed, L. H.: Studies on cerebrospinal fluid, Jr. Med. Res., 1914, xxvi, 21–111.
39. Jungeblut, C. W.: Power of normal human sera to inactivate virus of poliomyelitis in its relation to blood grouping and to exposure, Jr. Immunol., 1933, xxiv, 157.
40. Unpublished report of the Michigan Commission on Infantile Paralysis, 1931, 615 State Office Bldg., Lansing, Michigan.

VIRUS DISEASES OF ANIMALS TRANSMISSIBLE TO MAN *

By K. F. Meyer, *San Francisco, California*

Infections or diseases of animals associated with or due to incitants generally designated as viruses, since 1892, have attracted more and more attention. In fact, these maladies, single or in epidemic distribution, have assumed an important position in the realm of the heterogeneous infection chains.

The insect-borne diseases, yellow fever, dengue, pappataci fever, Rift Valley fever, etc., are caused by filterable incitants, which localize and multiply in the poikilothermic hosts and, consequently, are classed with the heterogeneous infections. Between the causative agent of the disease and the poikilothermic host, a specific mutual relationship exists and the insect (mosquito) is not merely a vector or transmitter but a definite host. A well regulated cyclic organization continuously shifts the relative position of man and insect. As far as the available information indicates, the disease incitant is never transmitted from man to man nor is it spread from insect to insect. Doubtless the continuous change between vastly different hosts must be accompanied by alterations in the biologic activities of the virus of the disease concerning which very little is known. Of interest is the further observation that the vector is slightly, if at all, affected by the virus. For the preservation of the parasite, this behavior is of the greatest importance. Should the vector succumb to the disease incitant or should the desire to suck blood disappear, then the transmission to man would cease and the chain would be regularly broken in the insect. In due course, the disease would become rarer and finally disappear entirely.

There is a second and decidedly larger group of infectious diseases, which may be conveyed from warm blooded animals either by the percutaneous, the alimentary or the permucosal routes to man. This group comprises virus infections, which are quite variable with respect to their localization, portal of entry and mode of transmission. Some of the incitants responsible for the diseases of this group possess a broad pathogenicity range; they are capable of infecting, in nature and experimentally, a great many hosts. Thus in nature, rabies is confined to a comparatively small number of species, dogs, cats, coyotes, foxes, wolves, jackals, horses, cattle, pigs, deer and moose, but artificial transmission is possible among a wide range of animals. In fact it may be assumed that no mammal or even bird is insusceptible. As a rule, the infection chains are broken following the first transmission to man. The restricted mode of natural transmission—percutaneous introduction of the virus through a bite wound as in rabies

* Read at the Chicago meeting of the American College of Physicians, April 16, 1934.
From the George Williams Hooper Foundation, University of California, San Francisco, California.

—is in part responsible for this behavior. A change of host, as for example a transfer to man, will sooner or later lead to a blind ending of the chain. A continuous passage in the animal host is obviously an absolute necessity. In some of the infections in man the clinical and anatomical characteristics are identical with those of the disease in animals. The neurotropism of the rabies and louping-ill virus is fully preserved. On the other hand, pulmonary manifestations are rarely seen in psittacine birds suffering from psittacosis, while they are the prominent symptom in the clinically recognized human infections with this particular virus.

Although it is the purpose of this paper to outline the effects of certain viruses, it may be permissible to inquire quite briefly into their nature. By usage, the term filterable virus is applied to a noxious agent or poison susceptible of being passed through a diatomaceous earth or kaolin filter impervious to ordinary bacteria. To a certain extent, this term is misleading since bacteria and spirochetes have been found capable of penetrating such filters; and a few incitants and the diseases caused by them have been placed with the filterable viruses even though they have not been shown to be filterable or only pass the filters with difficulty (rabies). The numerous painstaking studies of recent years have shown that many of the viruses are not merely enzymes or transmissible mutagens as was originally intimated by Beijernick's description of the tobacco mosaic disease as a *contagium vivum fluidum*. In fact the evidence secured by special staining procedures (Borrel, Paschen, Goodpasture and Woodruft, Cowdry and others), dark field-ultraviolet microphotography (Barnard), differential centrifugalization (Bechhold and Schlesinger, Eagles and Ledingham, Bedson), ultrafiltration (Bechhold, Krueger, Elford), immunity reactions (Smith, Ledingham, Andrewes) and photodynamic inactivation (Perdrau and others) indicates that the viruses are, in all probability, living infectious, biologically defined particles capable of reproducing themselves true to type. Their sizes vary from 10 to 170 $\mu\mu$. They are obligate cellular parasites but thus far no one has succeeded in growing them on lifeless media. Since they cannot regenerate in the absence of living cells, their existence is demonstrated by their activity in susceptible hosts. However, the immunity reactions, which are employed, reveal a remarkable relationship between bacteria and viruses. Antigenically different types of viruses may incite identical symptoms (several viruses are capable of producing encephalomyelitis). Further, the corpuscular infectious particles are specifically agglutinated by antisera (vaccinia) or the heated precipitable virus substance behaves like a hapten and incites skin reactions in the vaccinated human beings. In time these observations may be of aid in the preventive and curative aspects of the diseases caused by viruses but for the present the existence of such an agent is demonstrated by its activity in the natural and experimental host, in filtrates of tissues and in tissue cultures. The transmissible agents, in all probability animate in nature, are, therefore, judged by their activities and not by their morphologic or biochemical behavior.

Turning now to a consideration of the animal diseases caused by viruses transmissible to man, it may be profitable to confine the review to certain recent observations on rabies, Rift Valley fever and louping-ill, then to consider the problems regarding the possible transfer of foot and mouth disease, distemper and equine pernicious anemia to man and finally to discuss the psittacosis problem in the light of unpublished data collected in California.

Rabies

Although not a disease of any great consequence in the total mortality of animals and man, the fear inspiring character of the symptoms and its mode of transmission, so vividly described by Fracastorius (1546), continue to hold the imagination of the investigators. The study of the causative agent, the aberrant types of the viruses and the modifications of the Pasteurian treatment remain fascinating problems.

In the fall of 1931, I received from Professor Rosenbusch of Buenos Aires a sample of a glycerinated brain specimen of a rabbit, which had been injected with nerve tissues of a cow dead from "Mal de Caderas." According to the accompanying letter, a comparative test with the rabies virus was suggested. The specimen was inoculated into rabbits and found to behave like a rabies virus; typical Negri bodies were readily demonstrated in the hippocampus. Shortly afterwards, a communication was received from Dr. J. L. Pawan of Trinidad, who desired reprints and information concerning botulism in cattle. From a reprint of an article by Hurst and Pawan which was enclosed, it was noted that an epidemic affecting man and beast had appeared in Trinidad, and although the veterinary experts had diagnosed the disease in cattle as botulism, the evidence strongly pointed in the direction of a specific encephalomyelitis. Thus, an analysis of the relationship between the South American cattle and horse disease and the epidemic in Trinidad appeared desirable. Quite briefly, the facts established to date are as follows:

Since 1914, no case of rabies has been recognized in Trinidad, an island on which the strictest quarantine laws against rabies are in force. However, in 1929, cases among the human population simulating acute poliomyelitis made their appearance. Mainly children of school age were affected, and the 20 cases, which occurred in 1931, all ended fatally. The symptoms were those of paresis of the limbs, bowels and bladder, loss of sensation in the limbs and abdomen. A fatal termination ensued after an average of 8.5 days. The paresis followed an ascending course. Portions of brains sent to the Lister Institute, London, and to the Rockefeller Institute at New York produced on monkeys a virus infection indistinguishable from rabies. Negri bodies "Innen Körperchen" were regularly demonstrated. In the dog, the manifestations of paralysis predominate; those of biting are absent. Cross-immunity tests showed that the fixed virus protected in a certain number of cases against the intracerebral inoculation of the Trinidad virus, while immunization with the Trinidad virus protected

to a much lesser degree against the fixed virus. Results of serum neutralization tests showed evidence of a similar cross-immunity. Neuropathological lesions agree well with those recorded in cases of paralytic rabies. The anterior and posterior horns are equally affected, thus differing from the picture in poliomyelitis.

The features of the cattle disease were salivation, paresis of the legs, and a fatal termination after five or six days. A brain was sent to Hurst, who reported the presence of the rabies virus. The diagnosis of botulism had been based upon the clinical features of the cases, and upon the detection of the spores in the soil from the farms where cases had occurred. In two cows, the *Clostridium* was recovered from the liver and the spleen.

The epidemiological features of the human and cattle disease, both of which may be accepted as a form of rabies, are of greatest interest. In this connection, mention must be made of the reports by Haupt and Rehaag, who studied a cattle disease in Brazil as early as 1921, and of those of Costa and A. Costa and Rosenbusch in Argentine, and Migone in Paraguay during 1930 to 1933. These authors all agree that the disease is not contagious, has an incubation time of as long as two and one-half months, and is caused by the virus of rabies. Remlinger and Bailly, who tested the same virus as was sent to me, have definitely pronounced the Paraguayan virus to be a true rabies. On the other hand, Kraus and Duran, who experimented with the Trinidad and the South American virus, consider both to be varieties of the true rabies virus and designate it as *Paralyssa.*

Haupt and Rehaag were the first to establish the fact that the cattle had been bitten by vampire bats. In fact, the laboratory experiment of a bat biting a cow confirmed the supposition that these creatures were the vectors. In Trinidad, Dr. Pawan has demonstrated Negri bodies in the brain of a bat with unusual behavior. The occurrence of the cattle epidemics in the vicinity of wooded areas spoke in favor of a flying forest animal, the *vampire bat—Desmodus rufus*—and not the dog. A heifer, bitten 27 days before, died with symptoms of dumb rabies. The only human case at Trinidad, in which there was a history of a bite, occurred on July 6, 1931, and that was the bite of a bat. Symptoms developed on August 3, i.e. after 28 days. According to a more recent report, in three of the human cases mentioned by Hurst and Pawan, there was a definite history of a bite by a bat. Since this is not an uncommon occurrence in Trinidad, the investigators are of the opinion that final proof is lacking, although the evidence strongly incriminates the vampire bat as the transmitter of the disease. How the infection is spread among these mammals, and how they ever came in contact with a rabies virus remains a fascinating problem to be solved.

That rabies may show no tendency to spread among dogs is clearly shown by the observations made by du Toit in South Africa, who found that the yellow mongoose (*Cynictus penicillata*) and the genet (*Genetta felina*), two wild carnivora, have caused human infections. The presence of rabies has been confirmed by an examination of the brain of a sick mon-

goose caught in the veldt. How difficult the control of rabies may become, when the eradication of the transmitter is practically impossible, is well illustrated by these observations.

The statistical reviews on antirabic treatment continue to emphasize the relatively low proportion of neuroparalytic accidents following the use of dried or glycerinated cords. However, the incidence is still much greater than after treatment by killed carbolized vaccines. The subject of antirabic inoculation of dogs and domesticated animals with chloroform or phenol treated vaccines, or those fixed by passage from dog to dog has not crystallized into a unanimous verdict. Although declared safe and efficient, the methods can serve only as an aid in the control of an outbreak of rabies. In the United States, the elimination of the stray dog remains the major problem.

Rift Valley Fever or Enzootic Hepatitis

In 1931, Daubney, Hudson and Garnham described a virus disease affecting sheep, cattle and goats in the Rift Valley of the Kenya Colony. Very young lambs are highly susceptible, and a mortality of over 95 per cent has been observed. In ewes and cattle, the losses are relatively low. Anatomically, characteristic lesions, in the form of a focal necrosis resembling that of yellow fever, are regularly encountered. Infection through contact has not been observed, although the blood of the diseased animal readily conveys the malady by inoculation. Preliminary experiments and field observations suggest an insect, probably *Taeniorhynchus brevipalpis* as the vector. By moving the flocks of sheep from the mosquito belt to higher altitudes, the abortions and mortality in the ewes and lambs may be checked.

Not the least important point connected with Rift Valley fever is the fact that the virus is pathogenic for man. Four of the investigators who made the postmortems on the experimentally infected animals became infected. In every case the attack was characterized by a very brief period of general malaise, the temperature rose to about 103° F., persisted for 12 to 36 hours, and was followed by headache and pains in or near the joints. Every native engaged in the herding of sheep during the epidemic became ill for a period of four days. In fact, close to 200 human cases of Rift Valley disease without any fatality are known to have occurred. To prove the nature of the infection and to study its effect on a malarial infection, a man was injected with the diluted filtered virus. On the third day, he developed a febrile reaction and felt ill. Blood taken daily from the patient, infected lambs for a period of five days. Clinically, Rift Valley fever in man resembles sand fly three-day fever. It is differentiated from dengue fever by the fact that no rash, enlarged lymph-nodes or saddleback temperature chart accompanies the Rift Valley fever. Subclinical infections have been recognized with the aid of the complement fixation test. Incomplete evidence suggests the possibility that certain African rodents might serve as reservoirs.

Louping-Ill

For more than a century, a disease of sheep on farms in certain areas of Scotland has been discussed and attempts have been made to determine its etiology. Early in 1929, Pool, Brownlee and Wilson succeeded in experimentally reproducing the condition in sheep and pigs by inoculations of portions of the central nervous system from diseased animals. The infective agent, which is filterable, was also found occasionally in the blood.

Subsequently, it was shown by Gordon, Brownlee, Wilson and McLeod that the ticks (*Ixodes ricinus*), which transmit the virus, also harbor another infective agent which causes a febrile disease in sheep. However, the most important discovery was made by Alston and Gibson, who transmitted the virus to mice by intracerebral injections. Thus a means was made practicable for a more extended use of this virus for laboratory studies.

In this connection it is worth remembering that the investigators emphasized the high infectivity of the virus. Contact of uninoculated with infected mice resulted in cage transmissions. This infectiousness has now resulted in laboratory transmission to man. Rivers has recently studied such cases by neutralization tests and has shown that persons who have had intimate contact with the louping-ill virus either develop a definite encephalitis, an influenza-like disease, or pass through a cryptic infection. The literature reports no spontaneous cases of louping-ill among men in the regions in which the disease is common in sheep. These laboratory observations will doubtless lead to further inquiries.

Foot and Mouth Disease

The transmission of the virus to man must be considered as established, but its occurrence is quite rare. Despite numerous reports in the literature, undoubted cases characterized by an abrupt onset with fever, followed shortly by a vesicular eruption on the lips and mouth, the palms, soles and about the nails, and prompt recovery within two to four days, are few. Since a differential diagnosis cannot be made on clinical grounds, the reports of many exanthemata diagnosed as foot and mouth disease, without an infection or cross-immunity tests, are of little value. The susceptibility of man must be remarkably low, or otherwise it would be impossible to explain the absence of human infections following the use of small-pox vaccine contaminated with the foot and mouth disease virus. Thorshaug and Magnusson from Norway, and Motas from Rumania report such observations. The vaccine contained the foot and mouth disease virus in a highly virulent form and, when transferred to cattle and hogs, induced fatal infections. Equally convincing are the reports that only two proved human infections originated in the Institutes specially devoted to a study of the disease. To date, the number of human cases of foot and mouth disease, proved by transfer of the bleb content to susceptible animals, is, according to Trautwein, three (Pancera, Gerlach and Trautwein). The illness of a 25

year old caretaker, who accidentally cut his index finger on the right hand while infecting cattle with the foot and mouth disease virus, is particularly instructive. Two days after the accident, a small, burning bleb developed at the site of the already healed wound. Within two days, a multiple eruption appeared on both hands and feet. There was no rise in temperature nor general malaise. Within six days the blebs began to dry and about the sixteenth day after the onset, the crusts had fallen off. The contents of the blebs were tested on guinea pigs and a young pig. A type " B " foot and mouth disease virus was demonstrated. The blood of the convalescent contained neutralizing antibodies against the virus type " B," but not against type " A " or " C." Thus far, transmission from man to man has not been demonstrated; the infection chain is obviously broken.

Infectious Anemia of Horses

The transmissibility of the virus of infectious anemia of horses to man is of twofold interest. Although the only two human cases reported and proved refer to a German and a Dutch veterinarian, who both had intimate contact with diseased animals, it must be remembered that the virus may persist in the blood and tissues of horses for years and the affected animal may not appear anemic or sick. Since horses are used for the production of antisera for human use and since Koch has proved the contamination of sera with infectious anemia virus, it behooves the manufacturers of biologic products to select horses from areas in which swamp-fever has not been observed. The symptoms of one of the veterinarians, who had eaten infected horse flesh and had accidentally injured himself with an inoculation needle, consisted of headache, severe enteritis with blood in the stools, general weakness, emaciation, general pallor of the face and mucous membrane, and fever varying from 39 to 40° C. On two occasions, over a period of three years, the blood or the serum of the patient infected several horses after an incubation of from 26 to 39 days. Passage of the infective agent from horse to horse is readily accomplished. Thus it is conclusively proved that the virus of equine infectious anemia persisted in the body of a human being for at least three years. Another veterinarian suffered from severe anemia; his blood fatally infected three horses. These observations should be kept in mind and, particularly in the regions in which swamp-fever of horses is still prevalent (North Dakota, Nevada, Arkansas, Louisiana, Wyoming and Mississippi Valley), it would be desirable to test the blood of patients with obscure anemias by inoculating it into horses.

Dog Distemper

Dog distemper is a disease which can be transmitted to comparatively few animals. Until Nicolle experimentally inoculated a human being with the filtered virus and proved, by reverse injection of the man's blood, the persistence of the disease agent in the body without producing clinical manifestations, man was considered insusceptible. Is the explanation of Nicolle

correct? Did distemper originate as a disease of man which gradually, through hereditary transmission of a resistance, lost its pathogenic properties for man, only to be transferred to his intimate associate, the dog? Is it not unlikely that certain respiratory infections in man are due to distemper? What is the significance of the recent findings that human influenza may be transferred to ferrets, the most susceptible animals for canine distemper? One awaits with interest further studies which may deal with the solution of these intriguing questions.

The various pock diseases as virus infections should be considered under the general heading of this paper. Suffice it to recall that small-pox and all the animal poxes, except fowl-pox, are very closely related. In fact, it is probably correct to accept them as identical, and the variations which have been observed as merely adaptations to the particular animal with which they are associated. Each will, by passage through the calf, revert to the primal type, the cow-pox or vaccinia. The latter, as everybody knows, is readily transmissible to man, particularly through hands of milkers.

Psittacosis

In recent years a virus infection of birds, readily conferrable to man, has assumed a wide distribution in the United States. This disease is known as *parrot fever* or *psittacosis*.

The single and group infections, which followed the exposure to South American and African parrots previous to 1929, attracted little attention. As a part of the great pandemic which followed the distribution of diseased parrots from Argentine and Brazil, an extensive outbreak of psittacosis made its appearance in November 1929. Armstrong placed on record 74 foci of infection which gave rise to 169 cases with 33 deaths from November 23, 1929 to May 7, 1930. Today it is fully realized that birds other than South American parrots were involved in the epidemic of 1929 and 1930. In fact since December 1931, it is definitely proved that psittacosis is a common infection in the breeding establishments of California. The commercial distributions of shell parrakeets (*Melopsittacus undulatus*) throughout the United States has resulted in at least 156 human infections and a mortality of 30, or 19.2 per cent. Until the avian disease has been eradicated, it is not unlikely that physicians will have an opportunity to encounter this disease. A somewhat detailed review of the present day knowledge appears justified.

The Infective Agent. During the pandemic of 1929–1930 the virus character of the psittacosis disease agent was established by independent workers in England, Germany, the United States and France. Of particular importance was the discovery by Krumwiede, McGrath and Oldenbusch that the virus is readily transmitted to mice. The bacillus or *Salmonella psittacosis* has not been found in the course of the various studies conducted during recent years. In fact the extensive studies by Meyer and Eddie on several hundreds of infected shell parrakeets, and on the sputums

and organs of patients have proved the filterability of the disease incitant responsible for psittacosis. The virus is readily transmissible to white mice and various species of birds, in particular ricebirds and canaries. The fairly characteristic lesions produced in these animals are, as a rule, sterile but on microscopic examination reveal minute, Gram-negative ovoid or spherical bodies arranged in pairs and clusters. These corpuscular elements described independently by Levinthal, Cole, and Lillie are known as the L. C. L. bodies or "Rickettsia psittaci." Their constant presence in definitely virulent material from different sources and the fact that filters with a pore width of less than 1.9 μ usually retain the virus and thus indirectly define the particle size of the L. C. L. bodies are facts in favor of the interpretation of the minute corpuscular elements as the infectious agent of psittacosis. In the diagnosis of parrot fever the L. C. L. bodies possess the same value as Negri bodies in rabies. The virus is quite resistant to glycerine and under certain conditions to desiccation. However, it is readily destroyed by heat. In general, a strain of virus isolated from a parrakeet or a sputum may be passaged every six days. There is a tendency for certain strains to increase in virulence by passage in mice, but the virus does not become "fixed."

Birds Susceptible. It is now fully appreciated that not only parrots and parrakeets are susceptible to psittacosis but that the canary (*Serinus canaria*), bullfinch (*Pyorrhula vulgaris*), nonpareil (*Cyanospiza ciris*), Java sparrow (*Padda oryzivora*), cockateel (*Leptolophus hollandicus Kerr*), Bengalese (*Uroloncha acuticauda*), Pekin robin (*Liothrix luteus*) and even the common fowl (*Gallus gallus*) may contract the infection by exposure. Recent observations leave no doubt that parrotlets (*Psittacula conspicillata* and *Psittacula spengeli*) and conures (*Eupsittula pertinax*) imported from Colombia and the native shell parrakeet or budgerigar from Australia may harbor the virus in the spleen and liver.

Disease in Parrakeets. Shortly after the discovery of human psittacosis traced to California bred and raised shell parrakeets, a survey of the responsible aviaries was instituted. Visibly sick but mostly clinically healthy birds were autopsied and their organs, mostly spleens and livers, were tested for virus by intraperitoneal injections of mice. In acutely diseased birds the autopsy findings are as follows: A few drops of mucus on the ceres (nasal openings), a clean or soiled anus, thin, atrophic pectoral muscles, a large, heavy and tough, slightly saffron to ochre colored liver, occasionally (in about 10 per cent) studded with fresh or partially healed necroses and infarcts, slightly enlarged and congested spleen, rarely a few consolidated patches in the lower portions of one or both lobes of the lungs. The virus is readily demonstrated in the blood, brain and parenchymatous organs but not always in the nasal mucosa or content of the cloaca. The majority of birds examined, over 5,000, were the visibly healthy, well nourished shell parrakeets which had been chloroformed. The autopsy findings were essentially negative with the exception of a slightly or definitely enlarged spleen

which quite regularly contains the virus. The degree of latent psittacosis in shell parrakeets may be readily predicted by the percentage of spleens exceeding in diameter the normal average of 1 to 2 mm. Aside from the spleen and liver, the virus may be found in the ovaries and even the eggs. It is, therefore, not unlikely that the psittacosis virus may be transmitted congenitally.

Fifty-four, or 52 per cent, of 104 aviaries on which tests were made housed budgerigars with latent psittacosis. The percentage of virus carrying birds varied from 10 to 90 per cent. The virus leaves the body of the parrakeet (or other birds) by way of the cloaca and the nasal mucus. The cloacal content is very rich in virus when the birds exhibit signs of diarrhea or polyuria. In the course of these tests on the elimination of the virus it was found that the livers and spleens may be non-infectious, while the nasal mucosa may produce typical psittacosis lesions in mice. Obviously, recovered birds may harbor the virus in the nose for an indefinite period. The infectiousness of a parrakeet with psittacosis may be readily determined by placing in the same cage a pair of highly susceptible Java ricebirds.

Observations extending for several years have shown that avian psittacosis passes through an aviary about as follows: Many of the immature shell parrakeets contract the infection early in life; the disease is rarely fatal. Within one and a half to five months the birds may recover completely and possess a sterile immunity. The recovery from the infection may be indicated by an enlarged spleen. Young parrakeets may succumb to a relapse when transported in crowded cages or transferred into a cold climate. They are usually shedders of the virus and they may not only infect cage mates but human beings as well. Mature birds, eight months or older, are much more resistant and are seldom, if at all, involved in human outbreaks. Some may acquire a symptomless infection when exposed to shedding birds while others are entirely non-susceptible. The nature of this resistance is as yet unknown; it may be the result of a silent infection, or the result of a hereditary or maturation immunity. As far as preliminary studies indicate, the resistance is not associated with neutralizing humoral antibodies. Although the number of virus carrying birds and the danger of transmission of the infective agent to man progressively decrease with the age of the birds, it must always be remembered that the *incubation time* or the period which elapses between the injection of a shell parrakeet with virus or the exposure to carrier birds may be from 41 to 106 days. A small percentage of the old breeding birds, cocks and hens, continue to harbor the virus and thus maintain the disease in the aviary. While the breeding operations are discontinued, deaths from psittacosis may entirely cease, but as soon as they are resumed, the malady may reappear and spread among the young birds.

Human Psittacosis. In table 1 are presented the single cases or house epidemics which have been observed in the United States and Canada since 1929. One hundred and fifty cases had direct or indirect contact with diseased shell parrakeets either in California or in other parts of the United

States and Canada to which this species of bird had been shipped. During the same period infections, due to exposure to parrakeets from Cuba, the "Orient," Yokohama and Holland, have been recorded. In two, possibly three, cases the psittacosis infection was conveyed by canaries. At least three, in all probability six, cases were secondary human to human transmissions.

TABLE I

Psittacosis in the United States and Canada Due to California Parrakeets and Canaries

December 1929	San Francisco, Calif.	1 case
January 1930	Kansas City, Mo.	2 cases
March 1930	Victoria, B. C.	1 case
February 1931	Milwaukee, Wis.	1 fatal case
February 1931	Manitowoc, Wis.	1 fatal case
October 1931	Los Angeles, Calif.	1 case
November 1931	New York, N. Y.	3 cases with 1 death
November 1931	Los Angeles, Calif.	1 case
November 1931	Portland, Ore.	2 cases, 5 suspects, 2 deaths
December 1931	California	13 cases with 6 deaths
January 1, 1932 to December 31, 1932	*California*	39 cases with 4 deaths 2 cases due to contact with canaries
January 1932	Klamath Falls, Ore.	1 case
May 1932	Chicago, Ill.	1 fatal case
July 1932	Chicago, Ill.	3 cases with 1 death
August 1932	Coloma, Mich.	1 fatal case
September 1932	Several Counties in Minnesota	19 cases, 8 suspects, 1 death
October 1932	Boise, Idaho	1 case
October 1932	Malden, Mass.	2 cases with 1 death
October 1932	Troy, N. Y.	2 cases
October 1932	Madison, Wis.	12 cases
October 1932	Chicago, Ill.	1 case
January 1933 to December 1933	*California*	10 cases with 4 deaths
May 1933	Sioux Falls, S. D.	1 case
July 1933	New York, N. Y.	1 case
September 1933	Minnesota	1 case
October 1933	Connecticut	2 cases with 1 death
January 1934	New York, N. Y.	1 fatal case
February-March 1934	Pittsburgh, Pa.	6 (5) fatal cases (?)
	Total	130 cases 13 suspects and 30 deaths or a mortality of 19 per cent

Cases Due to Parrakeets from

Orient: April 1930	Vancouver, B. C.	9 cases
Yokohama: June 1930	New York, N. Y.	1 case
Cuba: January 1931	New York, N. Y.	5 cases with 2 deaths
Holland via Germany: February 1932	New York, N. Y.	2 cases

The clinical manifestations, which were recognized as early as 1879 as a definite entity, have repeated themselves with remarkable regularity and uniformity. The composite clinical picture, as seen in the 50 cases concerning which histories or personal observations are sufficiently complete for analysis, is as follows:

The incubation time, although in many instances difficult to establish, is definitely known for 15 cases and varied from seven to 14 days after initial contact. In three cases, a single exposure occurred and the incubation period was seven, eight and nine days respectively. In human to human transmission the interval between the onset of the illness and the discharge of the nurse was eight and 13 days respectively. Quite important is the observation that in a third case the transfer of the virus from a fatal infection in a woman to her nurse was 30 days after discharge from the case or 39 days after the last exposure to infected parrakeets. According to the published records, this must be considered an exceptionally long incubation period. The average is 10 days. As a rule, two to three weeks (average 14 days), but in a few instances three to four months, may lapse between the acquisition of the birds to the onset of the first case in a household (Ellicott and Halliday).

The onset has been mostly acute with chilliness, malaise and generalized pains, perhaps epistaxis. Prostration became marked during the first week and loss of appetite was always present. A temperature from 101 to 103° F. or above presented itself and at first aroused no anxiety. Toward the end of the first week, however, the disease became more severe. Vomiting and, in about 25 per cent of the cases, diarrhea have been reported. A slight but irritating cough was constantly present. The headache was more intense and the patient presented the picture of a severe illness, ate little, constantly demanded fluids and lost weight. Restlessness, depression, tremor and bad dreams were followed by stupor and delirium and other encephalitic symptoms. The tongue was invariably coated a dirty brown and signs of a pharyngitis have been noted regularly. Abdominal distention and constipation were seen, and in one or two cases roseolae appeared on the skin. The temperature maintained itself at a high level with slight morning remissions in the fatal cases or it was definitely remittent, yet the pulse showed only a slight increase and stayed at the beginning below 100. Auscultatory examination at the beginning of the second week revealed no definite signs. Later, crepitant râles which moved from one area to another, usually beginning in the left lower lobe, were established. In the few cases in which roentgen-ray pictures were taken, the peculiar homogeneous, slightly opaque density and contour, and migrating location of the pneumonic process suggested the diagnosis of psittacosis. A cough, increasing in severity, was always present in the severe cases but it was productive only in 65 per cent of the patients. The sputum was either tenacious, thick mucoid, or perhaps rusty and later definitely purulent. No chest pains were reported. Respiration and pulse were increased and the pneumonic process settled in a

definite area. Cyanosis and terminal pulmonary edema were seen in seven to 23 days after the onset. That the patient suffered from a very severe disease was amply attested by the pallor of the face, herpes labialis, bloodshot eyes, the semicomatose state only interrupted by delirious mutterings, restlessness and even violent excitement. Provided the pulmonary process was not too extensive, the patient's temperature dropped by lysis between the second to the fourth week. Recovery has invariably been slow and every patient complained of weakness and unsteadiness of gait for many weeks, even months. Relapses have been rare. Thrombotic-embolic processes were seen in one, possibly in two cases. Complicating bronchopneumonic infections, but in particular cardiac and vasomotor weakness, were responsible for the high mortality. A leukopenia (5,000 and 5,200) was noted in two of the 10 patients examined, while a normal count or a leukocytosis (17,200) was determined in the remainder of the group. A marked shift in the neutrophiles to the left was always present. Although in about 15 per cent of the cases, the clinical picture resembled that of typhoid fever, the spleen was not palpable and the liver descended only in one or two patients. Aside from the severe cases, mild even ambulatory cases in old and young people have been observed. In fact the clinical observations differ in no way from those recorded in connection with the exposure to parrots. No explanation can be offered for the noteworthy fact that the same degree of contact and the same virus may induce a disease of a varying degree of severity. It is not unlikely that the susceptibility of man is quite variable and that a fair percentage may be immune or pass readily through the disease in a latent and subclinical stage. Treatment of the cases has been symptomatic with particular attention to the heart. Dr. James B. Luckie has used leukocytic extracts hypodermically or intramuscularly. In some of the cases observed in the East, convalescent serums have been administered. The impression was gained that the disease was less severe but relapses were not prevented. Since weakly active neutralizing antibodies have been demonstrated in the convalescent human sera and since in some of the English cases antimeningococci serum and typhoid vaccine produced good results, it is quite likely that any agent which irritates the reticulo-endothelial cells is worthy of trial. However, mercurochrome in one case doubtless accelerated the fatal outcome.

In isolated cases, exposure to sick or dead parrakeets may induce clinical manifestations which in any one patient or in any stage of the malady are insufficiently characteristic to enable the physician to make a diagnosis. Various serologic tests for the enteric (*Salmonella psittacosis*) or undulant fever group of bacteria have been invariably negative, and it was merely the history of contact with parrakeets which finally aroused suspicion and led to a definite diagnosis. It may, therefore, be safely recommended that until the sale of non-infected birds can be guaranteed, it is well to be biased and to suspect psittacosis whenever a patient has recently brought psittacine birds or canaries into his or her household and suffers from severe influenza,

complicated by a migrating pneumonia. However, it is imperative that this suspicion or clinical diagnosis be confirmed, even though present laboratory methods frequently decide merely in retrospect. A definite laboratory diagnosis is also desirable for epidemiologic reasons. The majority of bird breeders, pet-shop owners, lovers of birds and even veterinarians still doubt the existence of such a disease as psittacosis.

The presence of the virus in the blood streams of patients has been established by Bedson and Western and by Meyer and Eddie. It has, however, been of little diagnostic value. In 28 clinical cases examined, the citrated blood of three patients infected mice when the blood was collected on the first, second and fourth days but not on the ninth, sixteenth or seventeenth days of illness. Since most of the patients rarely call a physician before the fifth or sixth day after the onset or at a time when the virus circulates irregularly, the mouse inoculation test with blood has been discontinued in California. However, the examination of sputums, first introduced by Rivers and Berry, has proved valuable. Since December 1931, Meyer and Eddie have tested the extracted, unfiltered but centrifuged sputums of 29 patients. A total of 42 sputum specimens has been examined. The virus was conclusively demonstrated in the sputum of 11 patients collected on the fifth, sixth, seventh, tenth, twelfth, fourteenth, sixteenth, twenty-third and thirty-seventh days respectively after the onset. One patient furnished a positive sputum on the fifth and on the tenth days but a negative one on the sixteenth day, while in a fatal case the excretion was infectious on the fourteenth, nineteenth and twenty-third days of the disease. In still another, the virus was found in the sputum on the tenth and thirteenth days. Seven of the nine cases observed in California since January 1933 had the nature of the infection proved by positive sputum findings. The failures to find the virus may be ascribed to the improper collection of the specimens late in the course of the infection. Since the virus is eliminated, irregularly repeated examinations on 24 hour specimens should be made. Microscopically, the secretion shows, as a rule, a few neutrophiles, lymphocytes and large alveolar epithelial cells. The autopsy material of six human cases revealed the virus in the lung, spleen and liver in three, while in the fourth, the spleen and liver were devoid of sufficient virus to infect mice. From two autopsies the organ specimens were sent in the same container, consequently, separate examinations could not be carried out.

Epidemiology. As might be expected, over 70 per cent of the human cases in California and elsewhere have been caused by newly acquired shell parrakeets. The majority of infections resulted from exposure to sick and, subsequently, dead budgerigars. These observations, together with the laboratory findings on the epidemic birds, indicate that the sick or dead parrakeets are more dangerous, largely on account of the liberal elimination of the virus through the nasal mucus and the droppings. The pathways of transmission of psittacosis from birds to man are probably twofold: (*a*) direct contact through the handling of the corpse of a bird which had died

of the disease, by feathers or excreta, by nasal discharge and through bite wounds; (b) indirect by the aerogenic route.

There is no doubt that the droppings and nasal discharges of the birds are readily scattered by the flying motions of the birds, which are easily agitated by the persons who handle or approach the cage. Air currents may disseminate the suspended virus particles. The environment of an infected group or of a single parrakeet may, therefore, be charged with virus and becomes a menace to human beings who may inhale it. It is, however, still a matter of conjecture whether the psittacosis virus in the droppings will regularly withstand prolonged drying and thus become dangerous. Furthermore, the possibility of infection by ingestion should not be ignored. Careful experiments are needed before a definite opinion can be expressed as to the importance of one or the other route. The high infectivity of the dispersed psittacosis virus, which resembles that of small-pox or measles, is shown in the histories in which a very short exposure occurred in a pet-shop where diseased birds were kept. It is, therefore, fully proved that, contrary to the general belief among the laity, actual contact or possession of parrakeets is not necessary. A brief visit in a room with birds or sojourn in a baggage car transporting birds may be followed by disease in the susceptible.

Case to case infections, already reported as early as 1898 by Leichtenstern and subsequently by Hegler, Hatfield, Sturdee and Scott, Armstrong, Ellicott and Halliday, and others, have been definitely proved in three cases in the California series. The evidence at hand strongly suggests a human to human transmission in three additional cases.

An interesting characteristic of psittacosis outbreaks is the occurrence in house epidemics. In three instances, man and wife, in a fourth, brother and sister, and in the fifth, several guests of the same household contracted psittacosis. This feature of multiple cases in the same house may be of diagnostic value (Barros).

In this connection consideration should be given to the *attack rates* in general. It is well known that heavy exposure, as for example, the employees in pet-shops or visitors in rural households, may be between 65 to 100 per cent. In occasional exposures the rate may be as low as 6 per cent. At the beginning of the investigation in California the bird breeders and the persons associated with the bird fancying trade pointed to their apparent immunity and, consequently, denied the existence of psittacosis. Logically, it was reasoned that a disease, alleged to be derived from parrakeets, would primarily attack those who are constantly in contact with these birds. Some credence was given to these arguments until systematic surveys not only proved the existence of psittacosis in aviary owners by laboratory tests, but revealed the fact that a history of a "severe attack of influenza with pneumonia" in bird breeders was occasionally elicited. It is naturally a matter of conjecture whether these "influenzal attacks" were true psittacosis or not. The fact remains that, of the 66 cases of psittacosis infections reported in California, 25 or 38 per cent were in owners of large or small parrakeet aviaries or in members of their families.

The great epidemics of the past, in particular the pandemic of 1929–1930, occurred during the winter months. Epidemiologists, therefore, have expressed the opinion that the prevailing disposition to respiratory infections, during the colder months of the year, favored the spread of psittacosis. There is little support to this interpretation in the California data as shown in chart 1. It is true that in December 1931 and in January and

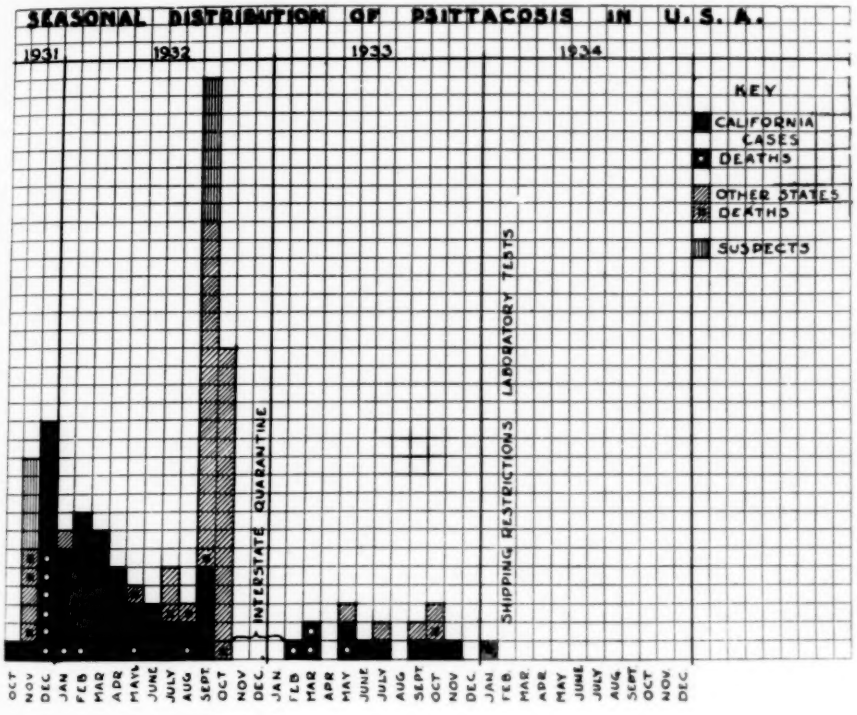


CHART 1.

February 1932, many new cases were recognized. However, it must be appreciated that shortly before these dates, a great many infected young birds were freely distributed for the Christmas holidays and a vigorous investigative campaign assisted in the location of cases, which would otherwise have been missed. By contrast, no cases were seen or reported during the very cold months of November or December 1932, or January 1933, when a complete inter- and intrastate quarantine paralyzed the traffic of parrakeets. There is, therefore, no support to the contention that the cold winter of 1931–1932 precipitated the outbreak. Scattered cases reappeared when the handling and shipping of birds were resumed. Many cases were seen in September and October and severe psittacosis is not uncommon in midsummer. It may, therefore, be concluded that the seasonal fluctuations are only influenced by the prevalence of infected birds. Usually, in the fall and early winter, immature carriers, sick birds and their mates, which cannot resist the vigors of transportation, reach their destination and are readily

capable of spreading psittacosis. The climatic factors are only of significance, as far as they affect the resistance of the birds, and the frequency with which human beings may be brought in contact with them through prolonged exposure in the closed rooms of a winter household.

In chart 2 are set out 64 cases according to age. It will be noted that the majority occurred in middle age. The lower susceptibility of children is evidenced by the fact that only three cases under the age of 20 were re-

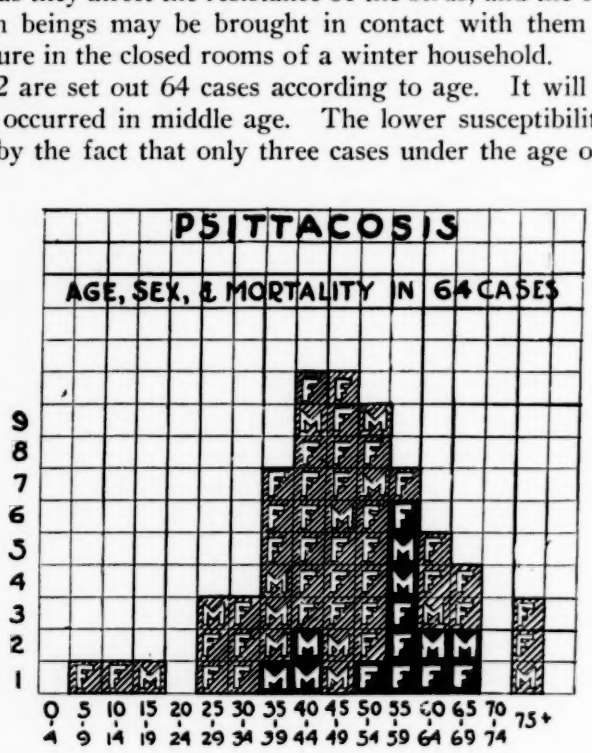


CHART 2.

ported. The youngest patient was 8½ years old and had a very mild attack. In the histories, intimate exposure of children to the same parrakeets which infected the parents or older relatives is repeatedly mentioned. As far as dependable investigations indicate, these contacts failed to produce disease in children. The sexes are unequally affected; 22 males and 44 females, or 66 per cent females in 66 cases. The greater frequency in females is, in part, due to the fact that they are either engaged in the breeding of parrakeets for their livelihood or as lovers of pets they come more closely in contact with the birds.

The case mortality rate in the 156 cases was 30, or 19.0 per cent, or for the California cases of the period 1931 to 1933, 67 cases with 14, or 21 per cent, deaths. No deaths took place below the age of 38. The rate corresponds closely with that determined by Armstrong (24 per cent for 167 cases) and Elkeles (20.9 per cent for 215 cases) as observed during the pandemic. Very much higher rates have been reported in the past. In one house epidemic in California the rate was 100 per cent. It appears reasonable that the systematic inquiries, which followed the discovery of one fatal

case, usually revealed one or two other milder cases, and thus helped to ameliorate the staggering mortality rate.

Protective Measures. Theoretically, psittacosis is a disease which could be easily controlled provided the public would appreciate the possible danger inherent in contact with birds, particularly of unknown origin. However, the love for pets so deeply rooted in human nature cannot be changed (Hasseltine). After nearly two years of struggle to accomplish some degree of protection by means of restrictive measures such as embargo and quarantine isolation, it becomes apparent that only one course is left open, namely, the systematic examination of the parrakeets by autopsies and laboratory tests and the destruction of the bird population of the aviaries housing infected budgerigars. This programme is now in process of execution. Time alone will tell whether it is possible to create breeding establishments free from psittacosis. Bird breeders and pet-shop owners, whose parrakeets have caused sickness and death, still declare in 1934 that psittacosis is an imaginary malady and the publicity a hysterical propaganda to injure their business.

In conclusion, it should be stated that the few examples were merely chosen to illustrate the complexities of a relatively new field of medicine. As a reservoir of human virus disease, the animal kingdom offers many intriguing possibilities and surprises.

UNDULANT FEVER*

By Joseph L. Miller, M.D., F.A.C.P., *Chicago, Illinois*

While we are not justified in calling undulant fever a new disease in this country, there is no doubt that of late there has been a great increase in its incidence. This I believe can be explained only in part by new interest in and consequent recognition of this disease. The character of the fever curve in many cases is so unlike that of any known fever, that it should have attracted the attention of physicians in the past.

A few imported cases were reported as early as 1897. C. F. Craig in 1904 reported the first recognized case acquired in this country. In 1926 46 cases were reported in the United States and in 1932, 1505 cases. One-third of all those reported in 1932 came from three states—California, Missouri, and New York.

The first appearance of this disease in epidemic form occurred in southwestern Texas. In 1913 it appeared in epidemic form in southern Arizona. Eight years elapsed before another epidemic was observed; this occurred in Phoenix, Arizona, in 1921. All of these arose from infected goats. Because it was restricted largely to goatherds and those who handled the goats during the kidding season, it is probable that contact, rather than milk, was responsible. It is reported that 25 years previous to the Texas epidemic there was a peculiar epidemic fever which received the popular name of goat fever.

If other cases of fever resembling that seen in this disease were observed in this country, they have not been reported with sufficient accuracy to enable one to claim that they were cases of undulant fever.

This disease had long been present in epidemic form in the Island of Malta. Sir David Bruce (1886) who was assigned to determine the nature of this infection was able to obtain, in smears of organs obtained at autopsy, a microörganism which later proved to be the etiologic agent. It was not, however, until 20 years later that the goat was recognized as the host. This was a chance finding. Animal experimental work was planned and, as the goat was the most readily available animal, six of these were secured for this purpose. A preliminary blood examination was made and it was found that five of the six goats agglutinated the microörganism isolated by Bruce in high titre. B. F. L. Bang in Germany isolated a similar microörganism from aborting cows in 1897, but it was not until 1918 that its pathogenicity to man was recognized. In German literature Bang's name is attached to this disease. In 1914 J. Traum isolated a microörganism from pigs with epidemic abortion.

There has been, and still is, considerable confusion in nomenclature. Alice Evans demonstrated that the microörganisms isolated from these three

* Read at the Chicago meeting of the American College of Physicians, April 20, 1934.

sources were identical as far as could be determined by ordinary cultural methods. In this discussion, *Brucella melitensis* is used for the caprine; *Brucella abortus* for the bovine; and *Brucella suis* for the porcine strain. Huddleson [1] by using different dyes in the culture media was able to differentiate these three strains. It might be mentioned that a microörganism similar in character has been isolated from horses, chickens, sheep, and, in one instance, from an aborting bitch.

The bovine strain is responsible for undulant fever in most city dwellers through the ingestion of infected milk. In packing house workers and among farmers, the suis variety is not infrequent, probably from contact infections. Hardy, Jordan, Boots, and Hardy [2] found the *Brucella suis* in 20 cultures from farmers, only one of whom had had close contact with hogs. They also obtained suis cultures in four farmers' wives. Hardy claims the suis variety may be found in cow's milk. He also states that it is much easier to obtain positive blood cultures in suis infections than in infections with abortus.

Considerable work has been done to determine the incidence of diseased cows, by the use of the agglutination test. Apparently, there is considerable difference of opinion as to what titre can be considered positive. Hardy considers a 1–80 titre as positive and a 1–40 as suspicious. When testing herds in Iowa he found, in 1300 cows tested, 26 per cent positive and 8 per cent doubtful. Dietrich and Bonynge [3] reported 36.7 per cent of 3000 cows in Los Angeles as being positive. Dr. C. P. Fitch (chief of the University of Minnesota Farm at St. Paul, Minn.) has tested all herds in scattered townships in Minnesota on the basis that a titre of 1–250 is positive and 1–150 suspicious. He has reported that 5.8 per cent of the cows in these areas were positive and 5.9 per cent suspicious. In 123 blood cultures from infected animals, only four were positive. In some herds he found over 20 per cent of the cows positive and 12 per cent suspicious. Starr [4] states that in the course of the two years, 1931–1932, 45,285 dairy cows were tested. Ten per cent were positive. In an abstract of his report, from which this information was obtained, no mention was made of the titre.

Fitch claims that at least 85 per cent of abortions in cows are due to the *B. abortus*. The disease, he believes, is spread by introducing a new infected cow into a herd. Between pregnancies the infection is apparently latent, but becomes active in the uterus during pregnancy and the cow aborts in the fifth to seventh month. As not all infected cows abort, absence of abortion is not evidence that the herd is free of infection. A bull may become infected from a cow and such infection is usually followed by orchitis.

The placenta and amniotic fluid are heavily infected and also the vaginal discharge which continues for about three weeks after abortion. It is Fitch's opinion that cows become infected from forage that has become contaminated by the amniotic fluid or vaginal discharge of diseased cows.

Calves nursing from infected mothers rarely show any evidence of infection, although the germs may be found in the feces. These discharges are probably another means of contaminating forage. It is the general opinion that the cow does not develop an immunity; that the disease is chronic with a latent period between pregnancies. Fitch states that in examining milk he has found that the gravity cream is most likely to contain the microörganism.

Incidence in Man

Four years ago Dr. A. V. Hardy, under the auspices of the National Institute of Health, made a survey of the entire state of Iowa to determine the incidence of undulant fever. He found 375 active cases widely disseminated throughout the state. Iowa is an agricultural state and 42 per cent of the inhabitants live on farms. In 10 instances he found more than one case in a family. In one instance an entire family of nine were infected. Seventy-seven per cent of the cases were males and 44.7 per cent of these were farmers. Among the women infected, 6.6 per cent were in farmers' families. Packing house employees showed the highest incidence. In a group of 100 positives who had no direct contact with live stock or fresh meat, it was presumed that the infection was acquired from raw dairy products. The disease was practically equally distributed between the two sexes—51 per cent male and 49 per cent female. The high incidence of males among farmers speaks strongly for the fact that the infection is acquired by direct contact.

Carpenter and Boak [5] determined that guinea pigs were easily infected by gently applying a culture on the bare skin at the base of the animal's ear. They found that infection with the porcine strain through this channel was more readily attained than with the bovine strain. When taken by mouth, the animal is more readily infected with the bovine strain. In the group where the infection took place, presumably by direct contact, 29 positive blood cultures were obtained and 24 of these were the suis strain. Attention has already been called to the greater ease with which blood cultures can be obtained in suis infection. From these observations, we may conclude that milk or the handling of raw meat is not the sole manner in which infection is transmitted.

Studies have been made to determine by the agglutination test the incidence of this disease in certain occupations. These results are of limited value because investigators have not been able to arrive at definite conclusions as to the minimum titre that may be called positive. If such a test is positive, it means only that the patient at some time has been infected.

Dible and Pownall [6] made a study of the agglutination test in packing house employees working on sheep, pigs, and cattle. They considered a titre of 1–40 positive. They found the highest incidence in those working with cattle; second, sheep handlers; and the lowest incidence in those working with hogs. Consequently, this indicates that infection may come from contact with sheep.

Veterinarians frequently show a high incidence of positive tests. In the great majority of those with positive tests there is no history of illness. There is abundant evidence that the agglutination test may be positive in the absence of any previous clinical manifestations. Huddleson and Johnson [7] tested 49 veterinarians. Of these, 57 per cent were positive and 26 per cent, in addition, had a positive agglutination in a titre of 1–100. Therefore, the total of positive or suspicious equals 83 per cent. Only three gave a definite previous history of undulant fever.

Thomsen [8] made a complement fixation test on 65 veterinarians and found 84.6 per cent positive. In none of these was there a previous history of infections.

A group of 18 veterinary students was examined—all were negative. Five months after entering practice 83.3 per cent were positive. In 16 bacteriologists working with Brucella 63 per cent were positive. In a group of 29 farmers 39 per cent were positive. In a group of 20 butchers 20 per cent were positive. As the complement fixation test alone was used on all this group, it is unwise to compare the results with those obtained by the agglutination method.

There has been some suspicion that the test may be positive in patients with typhoid fever. Bayne-Jones [9] made agglutination tests on 180 patients reported to have typhoid fever and all were negative.

There are a number of reports where all sera sent to municipal, state and private laboratories for Wassermann or agglutination tests have been tested by complement fixation or agglutination for evidence of Brucella infection.

Sasano, Caldwell, and Medlar [10] examined 1000 specimens by complement fixation—4.9 per cent were strongly positive; 4.7 per cent were weakly positive. In the agglutination test 4.1 per cent were positive in a titre of 1–45 or higher and 3.6 per cent positive in a titre of 1–15. In the 49 who gave a strongly positive complement fixation test, 36 also gave a positive agglutination. Four sera that gave a positive agglutination test in 1–45 to 1–135 gave negative complement fixation tests. Only five sera came from patients with clinical undulant fever.

Ruth Gilbert and Marion Coleman, in the laboratory of the New York State Health Department, examined 848 sera submitted for Wassermanns —0.4 per cent gave agglutination in 1–80 or higher. In 1186 sera submitted for agglutination test for typhoid 5.9 per cent gave a positive agglutination with Brucella, indicating that undulant fever may be mistaken for typhoid. In 1186 sera submitted as possible undulant fever, 11.5 per cent were positive. Just how many in this group were proved to be undulant fever is not known.

Meyers [11] in Nebraska tested 1000 sera submitted for Wassermanns. Of these 4.3 per cent were positive.

Hardy in his monograph has a very interesting report on agglutination tests on sera from various sources. These specimens came from the Iowa

State Laboratory and included sera for Wassermann and Widal; also sera from tuberculosis sanatoria; Iowa packing house employees; apparently healthy veterinarians; and from the Chicago Board of Health Laboratory. The sera from Iowa, submitted for Wassermanns, showed 9 per cent positive in a 1–20 titre; the sera from Chicago showed 1.5 per cent positive—showing the higher incidence of positive sera in Iowa. In the specimens submitted for Widal from Iowa 4.4 per cent were positive in a dilution of 1–20; specimens from 85 veterinarians showed 7.5 per cent positive in a dilution of 1–20, and 4.2 per cent positive in a dilution of 1–40—again showing a higher incidence as a result of contact infection. Inmates of a tuberculosis sanatorium showed 3.1 per cent positive in 1–40 and 2.9 per cent positive in 1–160 or higher—this might be accounted for by milk from an infected herd. The consumption of an unusual amount of milk would also increase the probability of infection. There are other reports showing an increased incidence of positive agglutination tests in tuberculosis patients. In the sera from 150 healthy packing house employees, he found a definite increase in positive titres—26.4 per cent were positive in a titre of 1–20 or more; 18.4 per cent positive in a titre of 1–40 or more; 7.8 per cent positive in a titre of 1–320 or higher; 1.3 per cent positive in a titre of 1–2500. The frequency of positive tests in high titre in people probably infected, but without present or past clinical history of any infection, indicates the restricted value of the agglutination test in determining the presence of an active infection.

A most interesting observation has been reported by Dooley [12] namely, that during an epidemic many of those using the infected milk may show high agglutination titre without symptoms. His observation was made in an Eastern boys' school where raw milk, from a private herd, was used. In 1925 epidemic abortions appeared in the herd, 12 cows aborting. Following this, any boy who had fever was given an agglutination test and this test was also given to many boys without fever. All tests were negative up to November 22, 1930. On that date one boy developed undulant fever and shortly after this a second boy. Investigation showed that one cow aborted on November 13 and that her milk was not used until November 18. This cow and four others which showed positive agglutination tests were removed from the herd and all milk was pasteurized. Following this, all the boys (232) and 31 adults were tested for undulant fever by the agglutination test—109 or 41.3 per cent were positive: 62 in a titre of 1–10 to 1–40; 32 in a titre of 1–80 to 1–160; 6 in a titre of 1–320 to 1–640; 5 in a titre of 1–1280 to 1–2560; and 4 in a titre of 1–5120 to 1–12,000. None of these boys had fever or were ill. The highest point in agglutination titre in this group was reached in January and February and after this the titre gradually fell. Eleven of those boys who had a titre of 1–10 to 1–40 later developed acute fever, chicken-pox, pertussis, sore throat, or febrile reaction after protective inoculation to typhoid. This was followed by an immediate rise in the agglutination titre. In one case

it rose from 1–80 to 1–640. This observation is of interest in that it shows the effect of an infection or febrile reaction on the specific titre.

We may draw the following conclusions from this observation:

First. Only 2 per cent of those infected had symptoms; the others were unaffected by the infection. If this be true, generally not more than 2 per cent of infected individuals are ill.

Second. A later mild febrile reaction may greatly increase the agglutination titre and might mislead the clinician into making a diagnosis of active undulant fever.

From a diagnostic standpoint, it is important to know how long a positive agglutination test may persist. There are several observations on this point which indicate that within six months, in some cases, the titre may be negative. In one series of 45 cases reported by Hardy, 30 were still positive in 1–40 after 12 months.

Onset and Symptoms

The incubation period varies from five to 15 days.

I know of no other acute infection in which there may be such a variety of symptoms, nor one in which there is such extreme variation in intensity and duration. The onset may be so mild, and the symptoms so insignificant, that the person is unaware that he has been ill. On no other basis can we explain the positive agglutination in people exposed to infections, but without any history of illness. The onset may be acute, with chill and those symptoms common to acute febrile diseases. The high fever may continue with intermissions for many years. The outstanding symptoms are a septic type of fever with frequently recurring chills and drenching sweats, especially at night. Very frequently, in fact an almost constant symptom, is arthralgia which in some cases may lead the physician to suspect he is dealing with an acute arthritis. Frequently there is abdominal distress, usually recurrent in character, which may be mild or severe and often localized. A considerable number of patients have been operated upon for appendicitis or cholecystitis.

The type of fever is extremely variable except that it always shows considerable daily fluctuation. The typical textbook wave-like undulating fever is not common. When present, it may persist throughout the course of the disease or be present inconstantly. Only rarely does the fever resemble typhoid, as the daily variation is more marked. The high septic type of fever may suddenly drop to normal, may remain so for days or for weeks, and then abruptly (often with a chill) re-assume its former characteristics. Not all patients, however, have this characteristic drop in temperature. In four of the seven cases I have seen, such drops in temperature have been noted. In one case, where the disease is now in its seventh year, the patient has had three cycles when the temperature disappeared for months. In one of these cycles the patient was afebrile for six months and gained 20 pounds in weight. The presence of this type of fever is not

observed in this country in any other disease and, when present, is of high diagnostic import. Rat-bite fever may be intermittent, but is quite different as it has one-day fever with three- to five-day afebrile periods.

Excessive sweats, without great impairment of the patient's appearance of well being, also are of diagnostic value. In the long continued cases the patients do not show the typhoid facies. It is true that they may lose in weight, but this is due to the high fever and consequent increased basal needs rather than to anorexia. Delirium is extremely rare, usually transitory and associated with hyperpyrexia. There may be high fever, but very moderate evidence of toxicity. The physical appearance of the patient may have high diagnostic significance.

Joint disturbance is another almost constant symptom. It has been present in all of my cases. There is subjective pain and tenderness, but no swelling in the mild cases. On the other hand, the joint manifestations may be so outstanding that they resemble those of acute rheumatic fever. If the patient has an afebrile period, the joint disturbance subsides in a large measure. In one of my cases the joint changes in the fingers had the characteristic spindle appearance seen in chronic rheumatoid arthritis and the condition had been so diagnosed. An intermission of the fever was followed by a disappearance of the joint swellings.

Suppuration of the costo-sternal and costo-chondral junction has been reported. Kulowski and Vinke [13] reported as a complication a suppurative spondylitis. Feldman and Olson [14] have observed similar changes in hogs affected with this disease and have obtained a pure culture of Brucella from the pus.

Gastrointestinal symptoms of a peculiar character may be present. Nausea may be a symptom in any severe infection and may be observed in patients ill with this disease. However, the symptom that has some diagnostic significance is pain, intermittent, usually somewhat localized, but not confined to any particular part of the abdomen. When the pain is present there is localized tenderness. It has been reported that this symptom is more frequently present early, but I have seen it present in a case where the disease was in its eleventh month. The presence of such a recurrent pain has diagnostic significance. Simpson and Bowers [15] have reported a number of patients with unrecognized undulant fever who have been operated upon for appendicitis or cholecystitis. The true cause of this pain has not been explained. An initial diarrhea has been reported; whether or not this ever persists, I have not been able to determine.

A prolonged septic type of fever, often with intermissions, arthralgia, profuse sweating, and intermittent gastric distress—when all are present—make it highly probable that the patient has undulant fever, even in the absence of a positive agglutination. Various complications may appear in the course of the disease, such as: mastitis, oöphoritis, and orchitis. One case with liver abscess has been reported and several cases with acute cholecystitis.

The pulse usually varies directly with the temperature. The spleen is usually, but not always, palpable. A slight, circumscribed macular or papular eruption has been described. Acute endocarditis, due to the Brucella, has been reported. As a result of prolonged fever, myocardial changes may develop and become manifest in the form of acute dilatation. In one of my cases, the patient developed acute dilatation of the right heart after eleven months of fever, without any preceding exertion to explain it. She recovered and at present has a competent heart. This same patient had also a fibrinous pericarditis.

Laboratory Findings

There is the usual secondary anemia. The leukocytes may be normal, or slightly increased in number, or there may be a leukopenia. In one of the cases in my series, during an unusual hyperpyrexia, the leukocytes reached 33,000. Considerable stress has been laid on the relative or absolute decrease in the polymorphonuclear cells. In patients with moderate leukocytosis, the percentage of mononuclear cells may equal the polymorphonuclear. This finding is of value when present, but it is not constant. One patient in my series never showed these blood changes.

Blood cultures when positive establish the diagnosis. Unfortunately, positive cultures can be obtained in only about 25 per cent of cases. So important is a positive blood culture that if, in a clinically suspicious case, it is negative it should be repeated several times.

Agglutination Test. In the absence of a typical clinical picture much stress has been placed upon the agglutination test. From observations recorded in this paper we can readily see the fallacy of accepting such a test as conclusive. The epidemic in the boys' school showed that those infected, but free from clinical manifestations, had a great increase in titre during a febrile reaction, due to any cause, which might lead a clinician to conclude that he was dealing with active undulant fever. Furthermore, it has been shown repeatedly that patients with this disease may have a positive blood culture and negative agglutination, or agglutination in very low titre. On the other hand, if we accept low titres as positive, we will find a considerable number of patients, especially in certain vocations, who, as a result of a symptomless previous infection, will give agglutination in low titre. The lesson to be learned from this is not to accept a positive agglutination if the patient's symptoms are not in accord with this diagnosis. If the patient's condition resembles an undulant fever clinically, do not abandon your clinical diagnosis even when there is a negative agglutination test, but continue to get repeated agglutination tests and blood cultures. Two of the patients in my series (one in whom the disease has been present for six years; the other, in whom it has been present for 11 months) clinically were cases of typical undulant fever. Early repeated blood cultures and agglutination tests, made by highly competent laboratories, were negative. Finally, after repeated agglutination tests, one of

the patients showed positive in 1–160, but a week later the agglutination test was again negative. The other patient, after repeated negative tests, was positive in 1–80; then again negative; and later again positive. This same phenomenon has been observed in the Widal test for typhoid. Another patient in my series showed the first positive agglutination test in the seventh week of the disease. It is obviously impossible to determine the minimum titre that may be pronounced positive.

It has been reported that the failure in the agglutination test might be due to the presence of different strains of Brucella. Hardy has checked up on this by using 46 strains, including both abortus and suis, and has found no variation in titre beyond the limits of experimental error. He occasionally found a recently isolated strain to be more resistant to agglutination, but this resistance disappeared after the fourth sub-culture. Marked zone phenomena have been observed. High titres may be positive with low titres negative.

Complement fixation test and intradermal tests are open to the same criticism and are, I believe, less dependable than the agglutination test.

The reduction in the ratio of the polymorphonuclear cells in the blood may be of great diagnostic value when positive, but of little value when negative.

Diagnosis

No attempt will be made here to discuss differential diagnoses. This has already been well done by others. From my limited experience, I believe that the diagnosis may be more difficult than in any other acute infectious disease. The recognized cases probably constitute only a small percentage of the persons infected. I only wish to emphasize the importance of accurate bed-side observation, using the laboratory as an aid.

Duration of the Disease

There is wide variation in the duration of the disease. The febrile period, in clinically recognized cases, may last only two or three weeks. In other cases the disease takes on a chronic form and continues for many years.

Mortality

The mortality, if we were able to diagnose sub-clinical cases, would be extremely low. In recognized cases it will average about 3 per cent.

Therapy

Preventive methods are now limited largely to the elimination of infected cows and the pasteurization of milk. Pasteurization is effective when properly applied. There is still considerable difference of opinion in regard to the titre in cows that may be considered positive. Probably cows vary in this respect the same as man. If these two methods of pre-

vention were carried out efficiently, we would still have the problem of contact infection, the elimination of which offers apparently insurmountable difficulties.

Experimental efforts to immunize cows against this disease have not been successful.

Active Treatment. Regarding active treatment one is inclined to believe with Hardy that "We find no record of a properly controlled systematic investigation in therapy." For this reason different forms of treatment will not be discussed in detail. The not infrequent sudden termination of the disease may readily deceive the therapeutist.

Vaccine therapy in cows, according to Fitch, is of no value. In man specific vaccine therapy is at present at a very low ebb. When vaccines are given in large doses subcutaneously, sufficient to cause a marked rise in temperature, or intravenously, with consequent febrile reaction, if results are obtained they are probably due to foreign protein therapy rather than the result of a specific vaccine.

Chemotherapy has failed.

Experimental work with serum therapy in guinea pigs has at best been only moderately successful. (See report of work of Gwatkin.[16]) Foshay has recently obtained a serum, by prolonged immunization of goats, which is promising. In a single case where I used it there was a prompt and permanent disappearance of the fever.

The literature contains several favorable reports following the use of typhoid vaccine intravenously. There are also some reports indicating favorable results following the use of arsphenamine.

With no specific treatment of proved value, general care of the patient is probably the most rational form of therapy. Bed rest, fresh air, nourishing food, with indicated symptomatic treatment, are important.

Summary

The incidence of this disease is probably much higher than reported cases would indicate. In blood submitted for the Wassermann test about 5 per cent of specimens show agglutination in moderate titre to Brucella. In many active cases it is impossible to get a positive agglutination test unless the test is repeated at frequent intervals. In long-continued cases the clinical signs and symptoms may be relied upon to make the diagnosis.

The best preventive measure is pasteurization of milk.

Among farmers the porcine type of infection is often found.

There is no proved satisfactory method of treatment.

REFERENCES

1. Huddleson, I. F.: Is *Bacterium abortus* pathogenic for human beings? Jr. Am. Med. Assoc., 1926, lxxxvi, 943–944.
2. Hardy, A. V., Jordan, C. F., Boots, I. H., and Hardy, G. C.: National Institute of Health Bulletin, No. 158.

3. DIETRICH, H., and BONYNGE, C. W.: Undulant fever in childhood, Jr. Pediat., 1932, i, 46–57.
4. STARR, L. E.: Va. Agricultural Exper. Station Bull. No. 48.
5. CARPENTER, C. M., and BOAK, R. A.: Undulant fever; sources, modes of infection and prophylaxis, Am. Jr. Med. Sci., 1933, clxxxv, 97–109.
6. DIBLE, J. H., and POWNALL, M.: Evidence of *Brucella abortus* infection in slaughter-house men, Am. Jr. Hygiene, 1932, xxxii, 347–353.
7. HUDDLESON, I. F., and JOHNSON, H. W.: Brucellosis; significance of Brucella agglutinins in blood of veterinarians, Jr. Am. Med. Assoc., 1930, xciv, 1905–1907.
8. THOMSEN, A.: Correlation of occupation with serologic reactions for *Brucella abortus*, Jr. Infect. Dis., 1930, xlviii, 484–497.
9. BAYNE-JONES, S.: Agglutination tests for the diagnosis of undulant fever, Am. Jr. Pub. Health, 1930, xx, 1313–1322.
10. SASANO, K. T., CALDWELL, D., and MEDLAR, E. M.: Complement fixation and agglutination tests in *Brucella abortus* infection, Jr. Infect. Dis., 1931, xlviii, 576–580.
11. MEYERS, J. W.: Jr. Prevent. Med., 1931, v, 240.
12. DOOLEY, P.: Undulant fever; epidemic of subclinical infection with Brucella, Arch. Int. Med., 1932, l, 373–379.
13. KULOWSKI, J., and VINKE, T. H.: Undulant (malta) fever spondylitis; report of case due to *Brucella melitensis*, bovine variety, surgically treated, Jr. Am. Med. Assoc., 1932, xcix, 1656–1659.
14. FELDMAN, W. H., and OLSON, C., JR.: Spondylitis of swine associated with bacteria of Brucella group, Arch. Path., 1933, xvi, 195–210.
15. SIMPSON, W. M., and BOWERS, L. G.: Surgical aspects of undulant fever, Am. Jr. Surg., 1929, vii, 597–604.
16. GWATKIN, R.: *Brucella abortus* infection in guinea-pigs; prevention and treatment with immune serum, Jr. Infect. Dis., 1933, liii, 230–236.

GONOCOCCAL ARTHRITIS: A CLINICAL STUDY OF 69 CASES *

By CHESTER S. KEEFER, M.D., F.A.C.P., and WALTER K. MYERS, M.D.,
Boston, Massachusetts

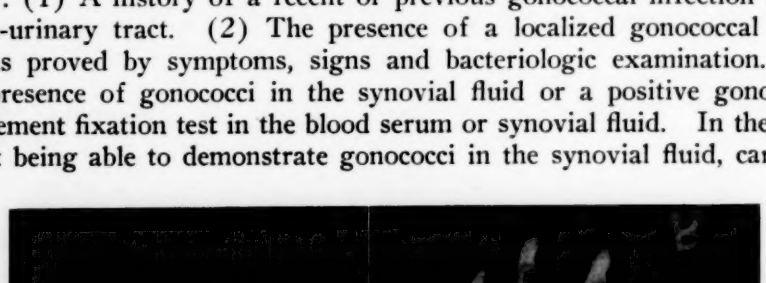
ONE of the commonest causes of acute and chronic arthritis is gonococcal infection. In many patients the diagnosis is a task of no small difficulty inasmuch as the arthritis may appear some weeks, months or years after the primary infection and, indeed, it may manifest itself for the first time after the original site of infection has healed entirely. In view of the frequent difficulty in diagnosis, we have analyzed the clinical features and course of the disease in 69 cases of gonococcal arthritis which we have observed during the past three years, in an attempt to emphasize a number of features which were helpful in establishing a diagnosis. In addition, we present data regarding prognosis in this disease.

Before proceeding with the detailed analyses of the cases, it is well to recall the pathologic features of the joint lesions in gonococcal arthritis. Elsewhere, Keefer, Parker and Myers [1] have described the histological picture of the synovial membrane in gonococcal arthritis. An appreciation of the changes is helpful in understanding the variations in the clinical picture and course of the disease so far as the joints are concerned. When there is pain, periarticular swelling and exudation of non-infected synovial fluid into the joint cavity, the pathologic process is confined for the most part to the synovial connective tissue where there are collections of polymorphonuclear leukocytes, lymphocytes and plasma cells about the blood vessels and between the strands of connective tissue. The cells upon the surface of the synovial membrane are intact and show no destruction. In these cases, it may be extremely difficult and, indeed, impossible to cultivate gonococci from the synovial fluid. In other cases, in which the synovial fluid contains numerous cells and organisms, there is an extensive inflammatory reaction of the synovial membrane and underlying connective tissue. When such is the case the superficial cells of the synovial membrane are destroyed entirely, leaving only a layer of granulation tissue with newly formed blood vessels, many polymorphonuclear leukocytes and numerous gonococci. The deeper layers of the synovial membrane may not be involved extensively but there may be destruction of the cartilage and underlying bone with a resulting fibrous or bony ankylosis. The destruction of cartilage and bone may occur within a short period of time following the onset of infection, and this feature frequently aids in the discrimination of gonococcal arthritis from other types of

* Received for publication June 1, 1934.
From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass.

chronic joint disease. Figure 1 illustrates the bone destruction that may occur in the metacarpal bone within a period of three weeks.

The diagnosis of gonococcal arthritis was made from the following points: (1) A history of a recent or previous gonococcal infection of the genito-urinary tract. (2) The presence of a localized gonococcal infection as proved by symptoms, signs and bacteriologic examination. (3) The presence of gonococci in the synovial fluid or a positive gonococcal complement fixation test in the blood serum or synovial fluid. In the event of not being able to demonstrate gonococci in the synovial fluid, care was



1 2

FIG. 1. (1) X-ray examination of right hand showing a normal joint space of metacarpal-phalangeal joint of the index finger. (2) X-ray of the same hand taken three weeks later showing destruction of bone, loss of joint space of the metacarpal-phalangeal joint of the index finger.

taken to exclude other types of arthritis such as rheumatic fever and tuberculous arthritis. In no case, however, was the diagnosis of gonococcal arthritis accepted without at least finding a localized gonococcal infection or a positive gonococcal complement fixation test on the blood sera or synovial fluid.

ANALYSIS OF CASES

Age. The age of the 69 patients varied from 18 to 70 years. Thirty-two of them were between 20 and 40 years.

Sex. There were 58 males; 11 females.

Color. Sixty-four were white, four were negroes and one was an Indian.

Previous Attacks of Arthritis. Twenty-one patients had had a previous attack of arthritis, and of these, 14 were definitely gonococcal arthritis. Of the remaining seven, three were due to acute rheumatic fever, and in

the other four the etiology was uncertain; it was stated that no urethritis existed at the time of the previous attack.

Previous Attacks of Gonorrhea. Thirty-four patients had had more than one attack of gonorrhea, and in seven additional cases the presence of a previous infection was probable. Fourteen of these patients had had gonococcal arthritis with their former attack of gonorrhea. This is a fairly high proportion in such a small number of cases, but it bears out the previously observed fact that recurrent attacks of arthritis are common with reinfection due to the gonococcus.

Time of Onset of Arthritis in Relation to the Gonorrhea. The evidence obtained as to the relation of the onset of arthritis to the stage of the initial lesion was not satisfactory in every case. This was due to the presence of a chronic genito-urinary tract infection of indeterminate duration or to inaccurate observations of the patients. In one, the arthritis began simultaneously with the appearance of an attack of urethritis; in eight, it appeared between 10 and 14 days after the onset of gonorrhea; in two, within three weeks; and in three, from two to six months. In the other cases the infection was either of indeterminate duration or there had been multiple attacks of gonorrhea so that the time relations could not be determined with accuracy. In three instances all traces of the local gonococcal infection had disappeared.

The observations indicate that arthritis may appear at any time after the onset of gonorrhea, commonly after reinfection, or rarely when the local genital tract lesion has disappeared.

Relation of Onset of Arthritis and Other Complications of Gonorrhea. There were 16 patients with bilateral catarrhal conjunctivitis (23.1 per cent) and three with unilateral iridocyclitis. Inasmuch as we did not see the patients until after the arthritis appeared and as, in some cases, the conjunctivitis gives rise to very few symptoms, the precise time relations between the onset of the arthritis and the ocular complications were difficult to determine. In two cases, the conjunctivitis appeared at the same time as the arthritis; in six, it had been present from one to 10 days before the onset of the joint pains, and in the others it was present at the time of the first examination and its duration could not be ascertained accurately. The conjunctivitis commonly disappeared within two weeks and before the joint pains. In only one case were relapses observed, and this was associated with a recurrence of an iridocyclitis. The discharge from the conjunctivae was scanty in amount and consisted of mucus containing leukocytes, but in no case were gonococci recovered from the exudate. Simple conjunctivitis always disappeared without any permanent damage to the eyes. Three patients had unilateral iridocyclitis, and conjunctivitis. This was extremely painful and produced a lesion resulting in diminution of vision.

One patient developed endocarditis; in this instance the arthritis pre-

ceded the signs of endocarditis but it was not clear how long vegetations had been present on the valves before the signs appeared.

Death occurred in four patients; in one there was an endocarditis, in another an intercurrent lobar pneumonia, in a third death resulted from a progressive gonococcal infection, and in the fourth there was a streptococcal septicemia.

Type and Extent of Local Gonococcal Lesion Associated with Arthritis. Of the patients with arthritis, 54 had prostatitis, 43 urethritis, 10 cervicitis, five epididymitis, one seminal vesiculitis, and one each an abscess of Cowper's glands, Bartholin's glands and Skene's glands. Three of the women were pregnant at the time of the infection, and in three no signs of a localized infection could be found. In men, it was the rule to find involvement of the posterior urethra and prostate when arthritis was present. In an occasional case, the onset of the arthritis could be definitely related to the extension of the local process to the prostate, epididymis or Cowper's gland.

Symptoms and Clinical Course. The first symptom complained of was usually pain in one or more of the joints, either the small joints of the hand, or the larger joints such as the knees or ankles. The pain was often first noticed to be dull and aching in character, exaggerated by motion, and then followed by swelling and redness. Of the 69 patients, the onset appeared after a respiratory infection in 10, and in these this history gave rise to considerable difficulty in diagnosis. The degree of swelling varied tremendously so that in 40 of the cases we were able to aspirate from five to 165 cubic centimeters of fluid from the joint cavities, and in 13 this was done more than once. The effusion into the joints varied in its duration; in 27 cases it diminished after one aspiration so that it was not necessary to do another; whereas in 13 it had to be repeated from two to 11 times. The pain was usually diminished markedly following aspiration of the joints.

Very often there was localized tenderness of the joints, especially, as in the knee, about the attachment of the quadriceps tendon to the patella and about the edge of the tibia.

Muscular atrophy in the neighborhood of the affected joints was observed in all cases, and in many it was extreme and out of all proportion to that which could be accounted for on a basis of disease alone.

Relaxation of ligaments and dislocation were not observed, but the deformities and restricted motion were due to contracture of the capsular tissues.

Joints Involved. Sixty patients had a polyarticular arthritis, and in the other nine it was monarticular. The joints that were involved are summarized in table 1. From this table it is seen that any or all of the joints may be attacked during the course of the infection. The olecranon bursa was involved once. A very common lesion when the ankles, wrists and metatarsal-phalangeal and metacarpal-phalangeal joints were the site

TABLE I

Joints Involved in 69 Cases of Gonococcal Arthritis

I. POLYARTHRITIS 60
II. MONARTHRITIS—Knee 9
Elbow 1

Joints		Tenosynovitis	
Knees	60		4
Ankles	34		25
Wrists	25		14
Metacarpal-phalangeal	18		6
Shoulders	17		
Metatarsal-phalangeal	16		6
Fingers	15		4
Hips	14		
Elbows	12		
Lumbar spine	11		
Toes	10		
Sacro-iliac	8		
Heels	7		
Cervical spine	4		
Dorsal spine	2		
Sterno-clavicular	2		
Costo-sternal	2		
Temporo-mandibular	1		
Olecranon bursa	1		

of infection was an associated tenosynovitis. This latter feature was outstanding in 33 cases and often it completely dominated the clinical picture. In one case, a localized tendon sheath abscess containing gonococci was seen.

Fever. An elevation of temperature above normal was observed in most of the patients. In some, it was of a few days' duration; in others, it was indeterminate and prolonged, varying from 99° to 100° or 101° F., and in a few cases reading as high as 102° to 103° F. In none of the cases was the temperature curve influenced by salicylates and there was nothing characteristic of the febrile reaction in the group as a whole.

Blood. The white blood cell count was increased in all cases, varying between 9,000 and 23,000 per cubic millimeter. The polymorphonuclear cells were increased and varied between 70 and 88 per cent. In the prolonged cases, an anemia frequently developed.

Sedimentation Reaction. The sedimentation rate was increased in all the cases, varying from 0.4 to 1.7 mm. per minute according to the method of Ernstene and O'Rourke. This examination was of no specific diagnostic value as we[2] pointed out previously. It was, however, helpful in following the course of the active infection.

The course of the disease was so variable that diagnostic difficulties often arose. In the acute cases, the differentiation from acute rheumatic fever was sometimes difficult, and in the subacute cases, the discrimination from rheumatoid arthritis was necessary.

The differentiation from acute rheumatic fever was especially difficult in the cases presenting a history of the onset of the arthritis following a

respiratory or tonsillar infection. In these, the onset of the joint pains was often acute, and it was only by observing the lack of responses to salicylates and the absence of changes in the cardiovascular system by physical or electrocardiographic examination, and by finding positive evidence of gonococcal infection that one could be reasonably certain of the diagnosis. In the subacute or chronic cases, the diagnosis was made only after the evidence for gonococcal arthritis had been obtained by repeated bacteriologic and serologic examinations.

The presence of bilateral conjunctivitis, perichondritis, iritis or tenosynovitis associated with arthritis that is progressive and deforming was suggestive of a gonococcal etiology and often helpful in diagnosis.

Prognosis. The prognosis in a given case of gonococcal arthritis is always difficult as far as the outcome is concerned. This is due, in part, to the extreme variation in the course of the disease and to a lack of information regarding the mechanism of recovery from gonococcal infection. Another factor of significance is the question of reinfection before the joint lesions have subsided completely. This was observed frequently and was followed in a large number of instances by an exacerbation of joint pains. In a previous paper,[3] we called attention to the fact that in patients who showed organisms in the synovial fluid and a cell count above 40,000 the outlook was poor compared with those with a non-infected fluid and a lower cell count. Even in such cases, the outlook is not very good as far as complete recovery is concerned, since only 37 per cent of our cases recovered completely without any signs of joint disease.

It can not be denied, then, that gonococcal arthritis is a serious disease. Factors that will influence the outcome are: (1) Severity of infection and reaction in the synovial cavities. (2) Persistence of local infection. (3) Reinfection.

Gonococcal Complement Fixation Tests. These were done on the blood serum of 52 patients and on the synovial fluid in 27. Of these cases in which the blood was examined, 45 specimens were positive (80 per cent), two were doubtful and five were negative. Of the cases in which the synovial fluid was tested, 20 or 74 per cent were positive. The principal diagnostic value of the test was in the cases in which organisms could not be recovered from the synovial fluid, or in the cases in which it was not possible to find organisms in the local process. This was the case in 11 instances.

Synovial Fluid. Information of considerable diagnostic value was obtained from examination of the synovial fluid, which was performed in 40 cases. For purposes of discussion they are divided into two groups, according as to whether the synovial fluid contained organisms or not. In the group of infected fluids, the total cell counts varied from 7,350 to 158,000 per cubic millimeter and for non-infected fluids from 1,800 to 78,250 per cubic millimeter. While the polymorphonuclear leukocytes predominated in both groups, they were usually higher in the infected than in

the non-infected group. In the latter cases, there were more lymphocytes, monocytes and clasmatocytes. In no instance, however, did they increase above 33 per cent. The chemical examinations of the fluid, including total protein, sugar and non-protein nitrogen, yielded no information of specific diagnostic value. The serologic examinations were detailed in the section dealing with the gonococcal complement fixation test.

Comment. From this analysis of 69 cases certain features require special comment. They can be discussed more clearly by reporting illustrative cases. We refer especially to the ocular complications, the presence of arthritis without evidence of localized genital infection, tenosynovitis, perichondritis and endocarditis.

Cases with Ocular Complications

Case I

Case of Bilateral Metastatic Conjunctivitis, Tenosynovitis and Arthritis.

A 31 year old white man was admitted to the hospital with the complaint of burning of both eyes and joint pains. An acute gonococcal urethritis had been present for one month. He had received anterior urethral irrigations of a 1–5000 solution of potassium permanganate. Ten days before entry both eyes became inflamed. There was intense burning and itching. There was little exudate from the conjunctival sacs. Repeated stained smears failed to disclose a gram-negative diplococcus. The conjunctivitis improved following boric acid irrigations and instillation of 0.5 per cent zinc sulphate. Seven days later, following a mild rigor, the left ankle became swollen, hot and tender. The right knee and right sacro-iliac region also became painful.

The patient had had an anterior urethritis due to the gonococcus nine years previously. There were no complications at that time.

On entry, the temperature was 99° F., the pulse rate was 90 per minute. The patient was well developed and well nourished, and acutely ill. Movement of the affected joints caused severe pain. There was edema of both eyelids and photophobia. The conjunctivae were only very slightly inflamed. There was a small amount of pus which could be expressed from the urethra. The prostate was tender, boggy in consistency and slightly increased in size. There was much swelling, increased heat and tenderness of the tendon sheaths about the left ankle. Movements of the ankle joint induced severe pain. Flexion of the left knee caused pain. Tenderness was elicited on pressure over the right sacro-iliac articulation.

Stained smears of the urethral pus revealed numerous intracellular gram-negative diplococci. The gonococcal complement fixation reaction on the blood was positive on three occasions. The Kahn and Wassermann reactions were negative. The leukocyte counts varied between 9,500 and 14,000 per cubic millimeter. Roentgenologic examination of the pelvis, knees and ankles showed no bone changes.

With local therapy the urethral discharge disappeared but the prostatic infection continued. The lower back pain persisted. About the left ankle, the increased heat and tenderness subsided gradually but slight swelling and pain on motion persisted. Pain on motion of the right ankle subsided. Swelling, redness and pain in the right fourth toe appeared the third week in the hospital, and later subsided somewhat. The patient left the hospital three months after entry. There remained slight tenderness over the right sacro-iliac articulation, slight swelling and tenderness about the left ankle and slight swelling and pain on motion of the right fourth toe.

This patient illustrates, then, two common complications of gonorrhea; namely, arthritis with tenosynovitis, and bilateral metastatic catarrhal conjunctivitis. The latter complication is by no means infrequent, and occurred in 23 per cent of our cases. It is called metastatic catarrrhal conjunctivitis in contrast to the purulent type which develops following the direct inoculation of the conjunctival sac with gonococci, and it must be carefully differentiated from this latter type since the prognosis in the two types is quite different.

While the metastatic conjunctivitis may be the only manifestation of a general infection, it is more often associated with other complications, such as arthritis; and for that reason its presence is of some diagnostic importance inasmuch as conjunctivitis is less common as a complication of other types of arthritis. It appears before, or simultaneously with, the arthritis. It is characterized by a bilateral injection and inflammation of the bulbar and ocular conjunctivae, with scanty mucoid discharge and slight subjective symptoms in comparison with the objective signs. The sequence of events in our cases was as follows: Following a localized gonorrhea, there appeared before, with or after the onset of arthritis a catarrhal inflammation of the ocular and bulbar conjunctivae. The upper lid was more often spared than the lower. In a few cases the lids were swollen and edema of the conjunctivae with chemosis of the bulbar portion appeared. The subjective symptoms were often minimal but burning, pricking, smarting, lacrimation and photophobia were frequent complaints. In all but three cases the process was benign, lasting about two weeks. In none of the cases were we able to recover gonococci from the exudate. The diagnosis was made on the presence of a gonorrhea, the absence of a history of infected material coming in contact with the eyes, the bilateral process, the mildness of the subjective symptoms in comparison with the objective signs, the scantiness of the exudate and the absence of gonococci.

In the three cases with iritis, the ocular manifestations were more severe. The following case illustrates the course of events in a man with iritis.

Case II

Case with Iridocyclitis and Arthritis.

A 30 year old white man entered the hospital because of painful swelling of the right knee and ankle and pain in the left knee. For two weeks, the patient had had mild lower back pain. Four days before entry, this disappeared; but there was redness, photophobia and lacrimation of the left eye. These symptoms subsided somewhat but there was blurring of the vision of the left eye. The right knee and right ankle had been acutely painful and swollen.

Gonococcal infection was denied. There had been a shrapnel wound of the right knee, with a subsequent operative procedure, five years previously. There were never any other joint lesions.

On entry the temperature was 100° F.; the pulse rate was 100 per minute. The patient was well nourished and well developed. He appeared acutely ill. The conjunctiva, iris, pupil and fundus of the right eye were normal. The left pupil was con-

tracted, fixed and irregular; there was marked circumcorneal injection; the pupillary space was cloudy; the fundus could not be seen. There was no urethral discharge. The prostate was tender and boggy in consistency. The capsule of the right knee was distended. The right ankle was swollen over the dorsal and lateral surfaces. Both joints were limited as to motion because of the severe pain. There was an increase in local heat but no redness about either joint.

The increased synovial fluid in the right knee was aspirated the day following admission. Ninety cubic centimeters of yellow turbid fluid, containing 52,800 cells per cubic millimeter, were removed. Ninety-eight per cent of the cells were polymorphonuclear cells and 2 per cent were lymphocytes. Fluid reaccumulated so that aspiration had to be repeated two and, again, four days later. The cells numbered 26,450 and 9,900 per cubic millimeter, respectively. The polymorphonuclear cells made up 98 and 99 per cent of the total, respectively. No organisms were recovered from these fluids on culture. The gonococcal complement fixation reaction of the fluids, as well as the blood sera, were positive. The Wassermann reaction was negative in the specimens of fluid and blood sera.

Soon after entry there was swelling, pain and tenderness of the left wrist joint. Fluid did not recur in the right knee. The left wrist and right ankle lesions subsided gradually. One month after entry pain and tenderness over the sacro-iliac articulations appeared rather suddenly, to persist for six weeks. Following a vigorous prostatic massage six weeks after entry there was a sudden appearance of fluid in the left knee joint with an exacerbation of the iridocyclitis of the left eye. Ninety cubic centimeters of yellow cloudy fluid were removed from the left knee joint. This fluid contained 13,300 cells, of which 92 per cent were polymorphonuclear cells, 5 per cent were clasmatocytes and 3 per cent were lymphocytes. The culture of this fluid did not yield a growth of microörganisms. Ten weeks after entry the patient still complained of pain in both knees, particularly on motion. The left wrist was painful on motion and slightly swollen. There was moderate swelling but little pain about the right ankle.

Following treatment, the left eye at first improved with loss of pain and lacrimation, and the partial return of vision. The conjunctiva was not inflamed. The pupil was dilated and regular. There was a recurrence of the symptom of iritis six weeks after entry as noted. Ten weeks after entry vision remained somewhat impaired, but no other symptoms remained.

Smears of the prostatic secretion revealed numerous gram-negative intracellular diplococci. The leukocyte counts varied between 7,800 and 15,000 per cubic millimeter. Roentgenologic examinations of the articulations showed evidence of synovitis but no bony changes.

Treatment consisted of instillates of a 1 per cent solution of atropine and boric acid irrigations of the left eye, light prostatic massage, forced fluid intake, bed rest, rest of the involved joints, massage and muscle-setting exercises.

In this case, the iridocyclitis was extremely painful, interfered with vision and left its mark in that there was permanent damage to the eye. There were relapses of both the arthritis and iridocyclitis while under observation, the cause of which remains unexplained. Whether the rigorous prostatic massage was responsible for a relapse remains an open question.

The ocular complications of gonorrhea have been discussed at length by Byers [4] in a most excellent and comprehensive monograph. He pointed out that the deep-seated congestion observed in some cases of conjunctivitis was often an expression of an inflammation of the interior structures of the eye. This is especially true when the uveal tract is involved, such

as we observed in the three cases of iridocyclitis. Byers emphasizes the fact that second and later attacks of uveitis are observed with recurrent attacks of gonorrhea. This also is true of attacks of arthritis.

Cases with Tenosynovitis and Perichondritis

Case III

Case of Arthritis and Tenosynovitis without Evidence of a Localized Genito-Urinary Infection.

A 21 year old man was admitted because of painful swollen joints. Five days before entry the patient sustained a slight laceration of the right thumb which required incision. Three days before admission he developed a sore throat, and swelling, pain, redness and increased local temperature of the knees and wrists. The following day, although the temperature was 104° F., the right knee and right wrist were asymptomatic. The left knee and left wrist continued swollen, red, painful and tender.

On entry the temperature was 98.6° F., and the pulse rate was 98 per minute. The patient appeared moderately ill. The pharynx was inflamed. The left knee was tender, hot and tensely swollen. There was evidently an increase in synovial fluid. The left hand and fingers were markedly swollen over the dorsal surface. Motion of the left hand and fingers or pressure caused considerable pain. There was no urethral discharge. The prostate was normal in size, shape and consistency. No prostatic fluid could be expressed.

The day following admission the synovial fluid of the left knee was aspirated. Eighty cubic centimeters of yellow cloudy fluid were removed with a cell count of 37,000 per cubic millimeter. The supra-vital preparation showed 86 per cent of polymorphonuclear cells, 12 per cent clasmatocytes and 1 per cent each of lymphocytes and monocytes. Two days later, the synovial fluid had reaccumulated and 80 cubic centimeters were removed. The cell count on this occasion was 14,300 per cubic millimeter, of which 94 per cent were polymorphonuclear cells, 3 per cent were clasmatocytes, 2 per cent were monocytes and 1 per cent was lymphocytes. The cultures of specimens of both these fluids yielded gram-negative diplococci which were identified as gonococci.

The gonococcal complement fixation reaction on the blood serum and synovial fluid during the first two weeks was negative. After the second week the gonococcal complement fixation reaction on the blood serum was consistently positive. The Kahn and Wassermann reactions were negative.

The swelling of the left knee did not recur following the second aspiration. However, the swelling of the dorsum of the left wrist and fingers persisted for two weeks before subsiding. Several superficial veins of the left forearm became thrombosed.

Treatment consisted of sedatives, bed rest, and splinting and local application of heat to the left wrist. The patient remained in the hospital for seven weeks. At the time of discharge there was limitation of complete flexion of the left wrist. There was no limitation of motion nor abnormalities of the left knee.

The outstanding features of this patient's illness were the absence of a history of gonorrhea, no clinical evidence of a urethritis, but a definite arthritis and tenosynovitis due to gonococcal infection. These observations emphasize the importance of a careful bacteriologic study of synovial fluid even in the absence of a history of gonorrhea or of the demonstration of a localized gonorrheal infection.

Case IV

Case with Tenosynovitis and Perichondritis of Cricoid Cartilage Associated with Arthritis.

A woman, 20 years of age, was admitted to the hospital complaining of pains in the joints of five days' duration. Two weeks before entry an abscess of the left Bartholin's gland appeared and three days later ruptured spontaneously. Four days before entry the right wrist became painful on motion and a swelling which was finally hot, red and very tender appeared on the dorsal surface of the wrist. The following day the left shoulder was sufficiently painful to prohibit motion of this arm. Two days before admission there was pain on swallowing and tenderness over the larynx. The left knee became painful the day of entry.

Four years previously the patient had been treated for gonorrhea for two months. Two years before the present illness there was an abscess of the left Bartholin's gland which ruptured spontaneously after one week. There had been no previous joint symptoms.

The patient was moderately obese and did not appear to be acutely ill. There was some injection of the pharynx. Pressure over the cricoid and thyroid cartilages caused pain, but there was no demonstrable swelling or redness. The dorsal surface of the right wrist was slightly swollen, red and tender. Motion of the right wrist and fingers caused pain in the area of swelling. Motion of the left shoulder, which was slightly swollen and tender, caused pain. There was tenderness over the left popliteal space.

Stained smears from the urethra and cervix contained numerous gram-negative intracellular diplococci. The gonococcal complement fixation reaction was doubtful on two occasions during the first week, and positive at the end of the second week of her stay in the hospital. The Kahn and Wassermann reactions were negative. The leukocyte count never exceeded 10,200 per cubic millimeter.

Soon after entry the palmar aspect of the right wrist became swollen and tender. Swelling and tenderness also appeared just above and posterior to the external malleolus of the left ankle. With rest in bed the symptoms subsided after 10 days. Three weeks after entry a small localized area of redness, tenderness and swelling appeared to the radial side of the distal end of the right ulna. On aspiration a small amount of purulent material was obtained which yielded on culture a gram-negative diplococcus. This was incised and drained. The patient was symptomatically improved at the time of discharge one month after entry.

This patient, then, illustrates two metastatic lesions of gonorrhea aside from arthritis; tenosynovitis which finally localized with abscess formation and a perichondritis of the cricoid cartilage.

Tenosynovitis is a particularly common complication of gonorrhea and, while it is usually an accompaniment of all types of arthritis, it occasionally occurs independently. For these reasons, its presence is often suggestive of the diagnosis of gonococcal infection. It was present in 43 per cent of the cases. (See table 1.) The tendon sheaths most frequently involved were those about the internal and external malleoli, and those over the dorsum of the hands and feet. In four patients, there was involvement of the tendons about the knee joints. Aside from these tendons, those of the palm of the hand and the Achilles tendon may be involved. (Strandberg.[5]) The clinical features are quite striking, in that the skin over the tendon sheaths is swollen, hot, tense, shiny, and any movement or pressure of the affected part is accompanied by agonizing pain and discomfort.

Rarely, as in case 4, there is suppuration and it becomes necessary to incise and drain the affected part.

Perichondritis of the cricoid cartilage was a feature in case 4, and in one other patient. This complication is observed in an occasional case and one's attention is attracted to it by the patient's complaint of both painful and difficult swallowing. Pressure over the affected cartilages produces pain and discomfort, and lateral motion is particularly apt to be painful. Occasionally there is swelling and redness. Besides the involvement of the laryngeal cartilages, the concha of the ear and the cartilages of the ribs may be the site of inflammation. Of our cases, two showed pain and tenderness over the costo-sternal junctions, and this did not progress to suppuration.

These two complications, then, tenosynovitis and perichondritis, may suggest the diagnosis of gonococcal infection, especially if they are accompanied by arthritis.

Another complication of gonorrhea is endocarditis, and when it occurs in association with arthritis the etiologic diagnosis may give rise to some confusion and difficulty. The sudden appearance of cardiac murmur due to ulceration of the valves may, however, give important aid in the diagnosis. This was so in case 5.

Case V

Case with Gonococcal Polyarthritis; Tenosynovitis and Ulcerative Endocarditis without Obvious Portal of Entry.

A negress, 28 years of age, was admitted to the hospital with the complaint of pains in the joints. Six days before entry she developed pain in the metacarpal-phalangeal articulation of the left thumb. Two days later both shoulders, the right elbow, the left wrist and the left knee were also painful, tender and warm. All joints had subsided before entry except the left wrist and the metacarpal-phalangeal articulation of the left thumb. There had been profuse recurrent sweating and general sensation of fever for four days.

The patient denied the symptoms characteristic of an acute genito-urinary infection by the gonococcus. There had been moderately severe dysmenorrhea and profuse yellow vaginal discharge for one year. The menstrual period had begun eight days before entry and profuse bleeding continued.

On admission the temperature was 102° F., the pulse rate was 26 per minute. The patient was a well developed and well nourished negress who appeared moderately ill. There were small lymph nodes palpable in the anterior cervical and inguinal regions. The tongue was coated. The tonsils and pharynx were somewhat injected. The examination of the chest and lungs revealed no abnormality. The heart was of normal size to percussion; the first sound at the apex was accentuated; no murmurs were detected. The systolic blood pressure was 115 mm. of Hg, and the diastolic level was 70 mm. of Hg. Examination of the abdomen revealed no abnormalities. The external genitalia were normal. Pelvic examination was not done because of vaginal bleeding. The dorsal aspect of the left wrist showed swelling, tenderness, increased heat and redness. The swelling followed the outline of the tendon sheaths. The base of the left thumb and the left thenar eminence was red, painful, tender and hot. Motion of the thumb caused considerable pain.

The patient remained in the hospital for 18 days before death. The temperature

showed daily variations between 98° F. and 104.6° F. There was profuse sweating but no associated chills. The symptoms and signs referable to the joints and tendon sheaths varied little. On the second day after entry there was heard over the base of the heart a diastolic murmur which, as time passed by, became louder, rougher and was eventually radiated over the whole of the precordium. Three days before death the systolic blood pressure was 114 mm. of Hg, and the diastolic level was 44 mm. of Hg. The classical signs of aortic regurgitation were noted. There were no embolic phenomena. Uterine cervical smears revealed no gram-negative diplococci. The gonococcal complement fixation test on the blood serum was repeatedly positive. The blood Kahn, Wassermann and Hinton tests were also positive. Gonococci were grown from one of many cultures of venous blood. In spite of the administration of iron and ammonium citrate the hemoglobin remained under 60 per cent of normal. The leukocyte counts varied between 11,300 and 33,500 per cubic millimeter. The proportion of polymorphonuclear cells varied between 85 and 92 per cent.

The necropsy revealed an ulcerative endocarditis of the posterior cusp of the aortic valve; gonococci were demonstrated on culture of the vegetation. The fallopian tubes and ovaries were normal. The cervix was not examined.

In this patient, arthritis was the condition that caused the greatest discomfort at the onset and the ulceration of the aortic valves developed while she was under observation. There were no local signs of gonorrhea and even at autopsy no evidence of an active gonococcal infection of the genitourinary tract was found. That this is not an uncommon state of affairs is amply shown in Thayer's [6] cases in which the portal of entry could be demonstrated in only about one-half the fatal cases. The appearance of an ulcerative endocarditis during the course of an acute arthritis, especially if there is a tenosynovitis, should always lead one to suspect a gonococcal infection.

From these four cases, it is evident that a number of clinical features, aside from arthritis, may appear during the course of the gonococcal infection. In obscure cases of arthritis they may be of considerable assistance in establishing the diagnosis if they are present.

In addition to the clinical features of the disease, the bacteriologic, cytologic and serologic examinations of the blood and synovial fluid are of the highest importance in establishing a diagnosis.

Summary and Conclusions

1. The clinical features of 69 cases of gonococcal arthritis are presented.

2. Gonococcal arthritis is much more often polyarticular than monarticular.

3. The presence of an associated metastatic conjunctivitis, iritis, perichondritis, tenosynovitis and ulcerative endocarditis are often suggestive and helpful features in the diagnosis of gonococcal arthritis. Illustrative cases are presented to emphasize these points.

4. The cytologic, bacteriologic and serologic examinations of the synovial fluid were of the greatest value in diagnosis, and of less value in prognosis.

BIBLIOGRAPHY

1. KEEFER, C. S., PARKER, F., JR., and MYERS, W. K.: The histologic changes in the knee joint in various infections, Arch. Path., 1934, xviii, 199.
2. OPPEL, T. W., MYERS, W. K., and KEEFER, C. S.: Sedimentation rate of red blood cells in various types of arthritis, Jr. Clin. Invest., 1933, xii, 291–296.
3. MYERS, W. K., KEEFER, C. S., and HOLMES, W. F.: The characteristics of the synovial fluid in gonococcal arthritis, Jr. Clin. Invest., 1934, xiii, 767.
4. BYERS: The ocular complications of gonorrhea, Royal Victoria Hospital Reports, 1908, ii.
5. STRANDBERG, J.: Beitrag zur Kenntnis des sogenannten Tripperrheumatismus, Arch. f. Dermat. u. Syph., 1911, cvii, 177.
6. THAYER, W. S.: On the cardiac complications of gonorrhea, Johns Hopkins Hosp. Bull., 1922, xxxiii, 361–372.

A NEW TREATMENT FOR VARIOUS KINDS OF COMA *

By Dr. Richard Bauer, *Professor of Internal Medicine, University of Vienna*

Our knowledge of the chemical-physiological mechanism of death is incomplete. This mechanism is perhaps best understood in certain intoxications, in which the oxygen supply is disturbed, or in certain diseases of the brain, in which large areas of brain tissue are destroyed. We are little informed, however, as to the mechanism of death in the infectious diseases. We do not understand to what final factors death may be attributed in instances of cardiac diseases, carcinoma or tuberculosis. Quite unclear also remains at times the cause of death following various operative procedures.

Also the peculiar conditions of stupor and coma, frequently anteceding death, are as yet unexplained.

More knowledge of the chemical-physiological mechanism has been accumulated in instances of the diabetic, uremic, hepatic and pancreatic coma, and also in diseases of the suprarenals and hypophysis, although much awaits further explanation.

Thus, it is not surprising that the so-called hypochloremic coma was not known until 1927. We know now that hypochloremic coma is likely to arise, whenever dehydration and hypochloremia occur, followed by uremia and coma without any significant disturbance in kidney function. This occurs especially after a diet which is poor in NaCl, or follows a loss of body fluid in instances of diarrhea, vomiting, profuse perspiration, tapping, etc. At the same time an alkalosis is present, which explains the similarity of symptoms of alkali-intoxication and of hypochloremic coma.

Not long ago I [1] reported the case of a patient whose only clinical symptom was anuria. There was no renal pathology. After two days of relative well-being the patient went into coma and died. Autopsy revealed an extensive pancreatic necrosis but no significant kidney damage. The serum contained 400 mg. per cent of urea. This case represented a non-nephritic uremia apparently due to the anuria. Ambard recently expressed the belief that such an anuric uremia is not due to urinary retention, but occurs on the basis of a secondary protein breakdown.

In another case of pancreatic tumor the outstanding clinical symptom was persistent vomiting. The urine was free from NaCl and the blood showed considerable hypochloremia and a large amount of urea. The patient improved temporarily after NaCl administration. Two weeks later he developed coma and died.[2] The autopsy revealed a carcinoma of the body of the pancreas which had compressed the stomach and duodenum. As hypochloremia has been produced experimentally in pancreatic damage, the

* Read at the Chicago meeting of the American College of Physicians, April 18, 1934.

hypochloremia in this case may be explained not only on the basis of the persistent vomiting, but also on the basis of the pancreatic disease. In both of these cases death occurred with the symptoms of non-nephritic uremia.

May I proceed now to the results of my experience as to the treatment of such patients: An apparently healthy man suddenly took sick with severe dyspnea, which soon was followed by cyanosis, myocardial failure and enormous liver enlargement. The diagnosis at this time was adhesive pericarditis. The patient improved slightly under cardiac therapy but soon developed signs of uremia and slipped into coma. The blood contained 400 mg. per cent of urea. Because of previous good results which I have obtained with liver extract in patients with edema of the liver, this patient was given an intramuscular injection of Hepatrat (3 c.c.) (Nordmark Werke, Hamburg). Shortly thereafter the patient recovered from the coma and inquired about his condition with free sensorium. Although the uremia disappeared entirely, the patient finally died of myocardial failure.

Similar good results were obtained with liver extract administration in another patient aged 86, suffering from myocarditis, suburemia due to prostatic hypertrophy and myocardial failure. This patient lived for a year, during which time he felt well. Good results were also obtained in a case of septicemia.

E. Hammerschlag [3] reported similar good results in the following cases:

1. Liver disease of doubtful etiology, jaundice, diabetes, increased non-protein nitrogen, coma. Cured by liver extract injection.
2. Gastric tetany in duodenal ulcer; hypochloremia and uremia; improvement following NaCl administration. In spite of operation, uremia continued; it later subsided as the result of injection with liver extract. The patient died later as a result of peritonitis.
3. Acute gastro-enteritis, coma, no uremia, no hypochloremia. Cured with injection of liver extract.
4. Gastro-enteritis, jaundice, stupor. Uremia with normal chloremia. Septicemia with enterococcus. Cured with liver extract injection.
5. Empyema of the gall-bladder, coma. Operation could not be performed. Coma cleared up after liver extract injection.

Similar good results were obtained in instances of hyperemesis gravidarum, postoperative coma, extensive burns, etc.

It may be mentioned here that Robineau recently demonstrated that after operations there is an increase in urea and non-protein nitrogen in the blood. Considering the frequent presence of protein-resorption, the diminution of the intra-abdominal pressure which normally is directed toward the liver, and the circulatory failure, it becomes apparent that the danger of the occurrence of non-nephritic uremia in these cases is considerable.

The curative effect of liver extract injections in these cases is difficult to explain. I believe that the severe symptoms are due to a secondary breakdown of protein. This has been made probable by the studies of Ambard in cases of anuria. While in the hypochloremic conditions a protein breakdown frequently has been assumed, this seems to be certain only in toxic-septic conditions. In liver and pancreatic diseases the nitrogen metabolism is most likely disturbed. In hyperemesis, eclampsia and in postoperative conditions an increased protein breakdown is assumed. With the assumption in mind that the liver extract contains some liver specific constituents, perhaps hormones, the question arises whether an improved liver function might successfully counteract the consequences of an increased breakdown of proteins.

This question, I think, is to be answered in the affirmative. The action of the liver is diuretic and detoxicating. The liver converts NH_3 into urea, which in uremia may be excreted by way of the bile. The liver certainly also plays some part in the interrelationship with other glands.

An interesting point may be mentioned especially: During the process of breakdown of proteins there also occurs a breakdown of the nucleoproteids, which are converted in the liver into the nucleotids. Nucleotids are composed of either carbohydrate, phosphoric acid, guanin, adenin, or of carbohydrate, phosphoric acid and pyrimidins. While guanin and adenin are deaminized in the liver and oxidized to uric acid, the pyrimidins presumably are broken down in the liver into hydantoin and finally into carbon dioxide, urea and pyruvic acid. The pyrimidins contain the same nucleus as depressants such as veronal, amytal and luminal, while hydantoin contains the nucleus of nirvanol.

During the process of increased breakdown of proteins, the organism becomes overflooded with these substances. Although the liver is capable of converting the ammonia of the amino acids into urea, this organ is unable to get rid of the numerous products of the broken down proteins. Whenever the pyrimidin nucleus cannot be broken down any further, " autonarcosis " of the organism is likely to occur. The sudden dramatic improvement due to liver extract injection, as seen by Hammerschlag and myself, may well be explained by the assumption that the organism apparently is liberated from the broken down protein products, which have a narcotizing effect, as the result of the increased fermentative liver action. Ruskin considers possible such " auto-narcosis " in true nephritic uremia as well as in instances of the damaging action of the broken down nuclein in cases of nephrosis. According to Baudisch and Pfalz the pyrimidin breakdown is hastened by administration of iron. Ruskin, therefore, recommends in nephrosis the administration of iron, and stomach and liver substance in order to increase the hemoglobin content of the blood and to obtain an increased iron action. Liver administration in nephrosis, as recommended by Grossman years ago, has not proved successful, nor has liver extract injection real effect in true uremia. The rapid beneficial effect of

liver extract injection in non-nephritic uremia makes a fermentative, hormonal action all the more likely as most of the patients are not anemic. (See Ruskin.[4])

Quite recently sudden improvement following liver extract injection has been observed in post eclamptic coma. The comatose mother, as well as the asphyxiated comatose infant, were saved by this therapy. In view of the postoperative protein breakdown and the factors mentioned above, liver extract injections in postoperative patients are all the more to be recommended since this treatment also has been advocated in instances of postoperative thrombosis.

In spite of all these reflections it may be considered possible that the substances in liver extract which counteract the tendency to coma are not formed in the liver but only stored in it; like the " anti-pernicious " principle which is formed in the stomach but found in liver tissue.

REFERENCES

1. Bauer, R.: Urämie als Komplikation innerer Krankheiten, Wien. med. Wchnschr., 1932, lxxxii, 1286–1287.
2. Sitzung der Gesellschaft der Aerzte, Wien. klin. Wchnschr., 1933, xlvi, 860–863.
3. Hammerschlag, E.: Sitzung der Gesellschaft der Aerzte, Wien. klin. Wchnschr., 1933, xlvi, 1472.
4. Ruskin, S. L.: Acta pediatrica, 1933, xvi.

METABOLIC STIMULANTS WITH PARTICULAR REFERENCE TO SODIUM DINITROPHENOL *

By Edward L. Bortz, F.A.C.P., *Philadelphia, Pennsylvania*

Individuals coming to the medical service of The Lankenau Hospital with cardiac, nephritic, gastrointestinal, blood and other disorders, as well as diabetes and obesity, have been studied more and more in the nutritional section of the Metabolic Clinic. It is remarkable to note how many functional disturbances clear up when patients are placed on a sensible, restricted but adequate diet with the avoidance of coffee, tea, tobacco and alcohol. The writer has been interested for several years in the relationship of body weight to the optimum functioning of patients and has tried numerous methods to cause a reduction in adiposity.

The best system of weight reduction remains that of limit of intake of food and increase in output of energy. All cases ordinarily may reduce satisfactorily on restricted caloric intake but the perplexity arises when patients have restricted their food intake to a point as low as they themselves have a desire to coöperate with the physician. It comes then to the stage in the care of these patients where the doctor in charge must often resort to drugs to obtain further weight loss. For this reason great interest is being shown in the subject of metabolic stimulants and accelerants.

The Metabolic Coefficient

Metabolic activity is the utilization of the various nutritive elements for the maintenance of the fundamental physiological processes, the storing up of energy for later use, and the continuation of immediately vital functions. The ordinary source of materials is food, but metabolic processes continue whether or not the daily intake is adequate. If food is withheld a certain length of time, the body draws from its endogenous food supply. The nature of this supply is beyond control, fats and proteins being withdrawn in varying amounts according to their availability rather than to metabolic need.

It is of practical clinical importance to keep in mind also that there are two phases of metabolism, the anabolic or storing, or the creation of potential energy, and the catabolic or destroying, or the transformation to kinetic energy for physiological needs. The principal anabolic stimulant is insulin, which enables the body to withdraw sugar from the blood and store it in the liver and muscles; epinephrine plays an important part in the catabolic function by bringing about an immediate release of energy in the form of glycogen from the liver and muscles.

The metabolic fire, that is the vital force acting in the body, is subject to an infinite number of regulating mechanisms in the form of pro-enzymes,

* Read at the Chicago meeting of the American College of Physicians, April 17, 1934.

enzymes and anti-enzymes acting at various points in the process of chemical change. This system of enzyme control is responsible for the variation in metabolic coefficient, that is, in the degree of metabolic intensity which characterizes different species, different individuals within a species and the same individual at different times.

All physicians have had a considerable experience with the use of thyroid extract and are familiar with its action; more recently, this metabolic stimulant is falling into disuse, except on rare occasions where its assistance is required because of some glandular deficiency. Extracts of other endocrine glands, especially the gonads and pituitary, have been tried with more or less favorable results. The writer has been successful in moderate degree with the use of whole ovary in addition to diet, having obtained in some patients a loss of as much as 75 pounds.

As is well known, the hormones interact with each other, with the brain centers and the autonomic nervous system. They control to a large degree organic function and the body chemistry, so the increased oxidation following their use results from stimulation of several other physiological processes. It is the writer's impression that a distinction should be made between such agents and those which have the power *directly* to increase or decrease the rate of combustion. There is a definite class of chemical compounds which have this power, the best known of which are methylthionine chloride (methylene blue) and the dinitro compounds, on the one hand, and the cyanides on the other.

There is assuredly a difference between the condition of a subject whose metabolism has been stimulated by improving the quality of the blood, for instance, and one whose cellular combustion has been accelerated by the action of a chemical compound such as methylene blue. Theoretically, the variation in the metabolic coefficient caused by these chemicals may be assumed to be due to their effect on the sulfhydril-disulfide system, which is explained by Bory [1] as follows:

The five elements, nitrogen, carbon, hydrogen, oxygen and sulfur together constitute the foundation of the living edifice. Nitrogen and carbon are passive energy-potentials and remain inert until they are destroyed by the activity of the two opposed elements, hydrogen and oxygen. The rôle of sulfur in this process is to control, through its easily reversible reducing-oxidizing property, both hydrogen and oxygen to insure that neither will exceed the proper limit of activity. Sulfur, drawn principally from the amino acid cystine, combines with hydrogen in the tissues forming -SH; the -SH, or sulfhydril group, is readily oxidized, giving place to the disulfide group (S-S). The disulfide group is then reduced and the process repeated. The tissues producing the most hydrogen sulfide (H_2S) consume the most oxygen, and their carbon-nitrogen fund is destroyed in the combustion with the release of heat and energy.

Moreover, it is thought that in living tissues there is an enzyme or catalyzing substance which initiates, or accelerates, the hydrogenizing of

sulfur, thereby starting combustion when an increased amount of heat or energy is the immediate need of the organism. This happens naturally during physical exercise, when the body is exposed to a low external temperature and after the ingestion of food (specific dynamic action). Probably there is another substance, an anti-enzyme perhaps, which inhibits sulfur reduction and in this way slows or stops oxidation. Also, since the reversibility of the sulfhydril-disulfide system is known to be extremely sensitive to the pH of the tissues, it may be that the temporary acidosis caused by a poorly ventilated room directly slows the process of reduction and oxidation of sulfur.

It is not difficult to believe that the various metabolic accelerants which do not appear to disturb organic and nervous function while increasing the basal metabolism from 25 to 30 per cent have this catalyzing effect on the sulfur reducing mechanism and set in motion the whole train of events in the production of heat and energy, of an intensity commensurate with the dosage. With overdosage, the heat is generated faster than the heat regulating center is able to dissipate, there is a progressive rise in body temperature up to 115° Fahrenheit, and death occurs from heat rigor.

In accordance with this conception, a classification might be made as follows:

Metabolic stimulants—exciting or rousing the vital functions to activity
Metabolic depressants—lowering functional activity
Metabolic accelerants—increasing oxidation } without any appreciable effect on organic or nervous function
Metabolic retardants—decreasing oxidation }

The hormones, therefore, whether secreted within the body or administered artificially, the vitamins, the various "blood builders," drugs causing respiratory and circulatory stimulation, and perhaps even those promoting diuresis, should all be regarded as metabolic stimulants. Morphine, on the other hand, might be classified as a metabolic depressant acting through the nerve centers. The clinical condition of acidosis, of varied origin, acts as a metabolic depressant. It is difficult to determine the status of a drug such as quinine, which is said to hinder the action of the oxidizing ferments of both the blood and tissues, since the exact rôle of these ferments is not known.

Sodium Dinitrophenol 2–4

The most recently discovered metabolic accelerants are the dinitro compounds:

Dinitronaphthol
Dinitrocresol
Dinitrophenol.

The last two of these have already been commercialized and placed at the physician's disposal. Dinitrocresol has been studied in England by Dr. E. C. Dodds and his co-workers [2, 3] and is available for clinical use under the

trade name of "Dekrysil." Of particular interest to the clinicians of this country is dinitrophenol, the compound which has been so extensively studied by the investigators at Stanford University and is now being widely used in the treatment of obesity in the form of its sodium salt.

The history of the discovery and adaptation of the drug for clinical trial is so readily available in the current literature that it is unnecessary to repeat it here. Suffice it to say it has been proved that this chemical can increase metabolism to a high level without causing damage to vital organs and functions. The fundamental physiological phenomenon occurring when dinitrophenol enters the body is an extensive increase of the combustion which is neither directly nor indirectly the result of a stimulation of the nervous system. There is no relation to cardiac action or to increase in muscular work. The action is generalized and appears not to involve any special organ or body system. Extensive investigations have proved that the *usual* energy materials are burned independent of the type of diet. Nitrogen excretion remains normal and the fats are completely burned without giving rise to acidosis.

Clinical Experiments

For the purpose of determining the efficacy of sodium dinitrophenol as an accelerant of catabolism, clinical observations have been made in the Metabolic Clinic of the Lankenau Hospital on a series of patients, 35 of which serve as the basis for the present discussion. The series itself will be reported more fully at a later date. The majority of these patients were women and were selected more or less at random, making certain to keep in mind the published contraindications to the use of the drug. The patients studied had all previously been on reduction diets and had reduced as far as they themselves believed they could possibly go by dietary methods. In addition, about 35 per cent had taken thyroid extract or ovarian substance with variable results.

Each patient was given capsules containing 100 milligrams of the purified sodium dinitrophenol to be taken morning and evening after meals. After taking two capsules a day for a week, making certain that no ill effects were present, the dosage was increased to three capsules a day, one after each meal. From time to time basal metabolic readings, and blood, urine and other metabolic studies were made.

It is explained to the patients that the principal effect of the medication will be a sensation of warmth, perspiration and a loss of body weight. In the majority of cases the temperature did not rise over two full degrees Fahrenheit. The patients ate pretty much as they pleased. It is usually in the second week of therapy that patients complain of profuse perspiration and it is most important to warn them to avoid exposure to cold while perspiring. After ingestion of the drug for three weeks the temperature tends to approach normal and perspiration is less pronounced although loss in

weight continues. The basal metabolism is elevated from 12 to 40 points in practically all cases. Weight loss averaged three to six pounds during the first 10 days on one to three capsules of 100 milligrams each daily. In those individuals showing a physiological response to the drug, weight loss continued at the rate of one to four pounds each week for as long a period as the medication was kept up. In about one-third of the cases an additional loss of three to five pounds took place after cessation of the therapy, following which a level was reached where no further reduction occurred.

Toxic Effects

Hyperpyrexia
Dermatitis medicamentosa:
rash, pruritus, urticaria, hives
Jaundiced appearance due to staining of tissues and blood serum
Elevation of blood pressure
Pulmonary edema
Gastrointestinal reactions
General weakness; nervousness
Headache; dizziness
Exaggeration of psychoneurotic tendencies or of any pathological condition present
Toxic symptoms generally appear when the basal metabolic rate is raised above + 50%

Five of the 35 patients complained of minor symptoms such as urticaria, indigestion, nervousness, nausea and giddiness.

Two patients of the series developed what they interpreted as "pneumonia," one after taking two capsules a day for four days and the other after having been on the treatment from time to time for a few months; on physical examination of these cases at the time of the height of the fever, some râles were heard in the chest but no definite evidences of consolidation were diagnosed. There must have been at least moisture present but whether or not this was due to a respiratory infection per se, or was the effect of the drug as an irritant on the respiratory mucosa one cannot say.

One hypertensive subject developed a marked rise in both the systolic and diastolic pressure which to date it has been impossible to bring down to normal. On the other hand, a very obese male, weighing 380 pounds and with a notable endocrine dyscrasia, showed a great increase in sugar tolerance as his weight was reduced.

Another patient, who had developed a rather severe carbuncle just before the treatment was instituted showed the jaundiced appearance said to be due to staining of the blood serum and tissues with the drug.

Pain in the calf muscles was experienced in several cases.

One man on dinitrophenol twice a day for three weeks exhibited a slight urethral discharge which was non-specific in bacteriology; four years previously he had had a Neisserian infection.

Eight patients have had colds during the treatment.

Two stopped the medication because they disliked the sensation of warmth.

The most severe reaction was in a young woman, 24 years of age, weighing 160 pounds, with dysmenorrhea and evident glandular dysfunction. She was given one capsule a day for three days, two capsules a day for three days and then started on the regulation dose of three capsules a day after meals. Ten days after ingestion of the first capsule and after losing 3½ pounds in weight, she developed diarrhea, intestinal colic, generalized edema most prominent in the face and extremities, tingling and numbness of the extremities, and an urticarial rash extending from the forehead to the feet. The wheals were about the size of a half-dollar, elevated, red and radiat-

ing heat. The temperature was 102° Fahrenheit. The medication was discontinued, the patient was placed on a milk-toast diet, given calcium gluconate and a lotion for the itching. Within four to six days, the itching and rash had subsided and at the end of another week the patient was given one capsule a day with no ill effects; the dosage was gradually raised as in the first instance and five weeks after institution of the therapy, she had lost 10½ pounds, which she considered sufficient and discontinued the medication.

Most of the patients are losing weight consistently and like the treatment. Where there are no unfavorable reactions, they note an improvement in their general physical condition and have a desire for more activity. One of the concomitant effects of the drug is a general increase in well-being, a glow of the whole body, and a brightening of the mind. Since in these patients no other signs of toxicity have been noted, this is not likely a toxic effect.

Dosage

It may be possible that there are extremely susceptible individuals in whom even minute quantities of the drug may prove dangerous. The writer has not seen any such cases. Several fatalities and a number of untoward effects have been reported in the literature but in many cases either the dosage was too high or the dinitrophenol was not correctly administered.

To preserve the factor of safety, no patient should be given, at the onset of treatment, more than 100 milligrams a day for seven days. In the event that an idiosyncrasy is revealed, the development of serious consequences can be avoided by prompt withdrawal of the drug. If the patient exhibits no unfavorable symptoms on one capsule of 100 mg. per day for seven days, it is safe to increase the dose to two capsules and then to three capsules daily, which is the accepted therapeutic dose.

In the ordinary case, not more than 100 milligrams should be given at any one time, yet in a few cases in the present series larger doses have been given, exercising great care, with no apparent detriment to the patient. The highest dosage ever used was 200 milligrams four times daily.

Certain patients seem to be resistant to the drug and where there is no weight loss on the regulation dose, if the daily dosage is pushed beyond four capsules of 100 milligrams each, toxic symptoms, principally headache, vertigo and nausea, will develop.

Acute Intoxication

The use of dinitrophenol is too new for many cases of acute intoxication to have been reported but now that it is being dispensed by druggists without prescription, such intoxications are likely to be met with at any time and a definite, well thought out plan of procedure will be of value to the doctor called in to treat the case. Profiting by the experience of others [4-6] the writer would suggest the following measures as the most logical to resort to in handling an emergency of this kind:

1. Venesection (300 to 800 c.c.).
2. Intravenous injection of 100 to 300 grams of glucose in 1000 c.c. of physiological saline solution.
3. Insulin 5 to 15 units, repeated every two to four hours covered by glucose.
4. Orange juice, sugar cubes, fluids by mouth.
5. Cooling baths.
6. Oxygen therapy.
7. Morphine in sufficient dosage to allay the restlessness and apprehension.

Conclusions

From the author's experience it has been concluded that sodium dinitrophenol 2–4 is an accelerant of body metabolism capable of causing a notable reduction in weight. If used without regard to a planned diet, that is, a reduction diet of 700 to 1000 calories, weight loss will not be so striking although still taking place. One would get the impression that patients may be made to lose weight continually over as long a period of time as the drug is being taken and at a rate proportionate to the quantity ingested. Used with caution, this drug should prove to be a valuable adjunct in the treatment of those individuals who find it difficult or impossible to lose weight by the usual established method.

As might be expected dinitrophenol acts most satisfactorily in patients with the exogenous type of obesity. Individuals with pituitary or gonadal glandular deficiency often tolerate the drug badly or not at all. In two patients with mild myxedema, a heightening of thyroid activity approaching the thyreotoxic state has been noted after three weeks' medication; in this event immediate cessation of dinitrophenol therapy is imperative. This drug is not a substitute for thyroid extract.

It is exceedingly unfortunate for the laity that no law now exists to prevent the indiscriminate dispensing of powerful drugs such as the dinitro compounds. The therapeutic dose of 300 milligrams daily administered in three doses of 100 milligrams each is but one-tenth to one-third of that dispensed freely over drug counters today. We have knowledge of cases that have taken 15 to 30 times this quantity though not under the care of a private physician. One wonders how high the toll of deaths is going to mount when the beauty parlors and physical culture emporiums begin to pass it around. For the protection of the public, which is one of the principal responsibilities of the medical profession, and at the suggestion of an eminent jurist, the writer earnestly recommends that sodium dinitrophenol and allied chemical compounds be included in the list of dangerous drugs, the control of the use of which is governed by the Federal Food and Drug Law. These chemicals are not yet ready for general distribution through the medical profession of the country and it is unfortunate that druggists are insensitive to the fact.

That sodium dinitrophenol, dinitrocresol and other metabolic accelerants are of real value for the reduction of body weight in certain selected patients

who find it impossible to reduce by limitation of diet, is no doubt true. The writer, however, does not unreservedly recommend their use at this time and desires to stress that the safest and best way to lose weight is under the supervision of the doctor who will prescribe a diet adequate in all essential nutritive elements but limited in caloric value to such an extent that the patient's daily physiological needs will force him to draw on the fat reservoirs of the body. When the medical profession arouses itself to its obligation of service to those individuals requiring or wanting to reduce their body weight, and outlines a sensible régime to this end, the diet sanatoriums and quacks and charlatans will have a diminishing financial return and the general health of the community will be greatly benefited.

The author desires to express his sincere thanks for the helpful and critical coöperation and suggestions of his colleagues, Dr. Anthony Sindoni, Jr. and Miss Ethel May Hobson.

REFERENCES

1. Bory, L.: Le soufre et la nutrition, Presse méd., 1934, xlii, 348.
2. Dodds, E. C., and Pope, W. J.: Dinitro-o-cresol as stimulator of metabolism, Lancet, 1933, ii, 352–353.
3. Dodds, E. C., and Robertson, J. D.: Clinical applications of dinitro-o-cresol, Lancet, 1933, ii, 1137–1139, 1197–1198.
4. Perkins, R. G.: A study of the munitions intoxications in France, Pub. Health Rep., 1919, xxxiv, 2335.
5. Poole, F. E., and Haining, R. B.: Sudden death from dinitrophenol poisoning, Jr. Am. Med. Assoc., 1934, cii, 1141.
6. Tainter, M. L., and Wood, D. A.: A case of fatal dinitrophenol poisoning, Jr. Am. Med. Assoc., 1934, cii, 1147.

BLOOD CHOLESTEROL AND CREATINE EXCRETION IN THE URINE AS AIDS TO DIAGNOSIS AND TREATMENT OF HYPOTHYROIDISM *

By JULIUS H. HESS, F.A.C.P., *Chicago, Illinois*

THE clinical symptoms of diminished thyroid activity in their classical form, during infancy and childhood, are too well known to bear repetition. One of the most important problems in the care and treatment of congenital or acquired hypothyroidism during childhood is early recognition. It is reasonable to assume that the longer treatment is delayed, the less opportunity there is of attaining the most desirable therapeutic result. Until recent years, physical signs, clinical symptoms, and basal metabolism determinations were the most important methods of establishing the diagnosis of hypothyroidism.

In infants and children, the characteristic physical appearance, subnormal temperature, retardation of growth, and other well known symptoms of hypothyroidism present a striking clinical picture. The classical symptoms and physical appearance are not, however, always present in early infancy and the clinically questionable cases in older children make it desirable to have additional aids in diagnosis.

Basal metabolism determinations have been of invaluable aid in assessing thyroid activity in older children and in adults. The limitation of basal metabolism determinations in children below the age of eight is, however, apparent when we consider that in most cases this can be accurately carried out only by direct calorimetry (measuring heat production directly in a closed chamber). Such an apparatus is not ordinarily available to the physician. Even in older children, the lack of coöperation due to mental retardation, excitement, or nervousness often renders the test unsatisfactory in obtaining reliable information.

For the past year we have been interested in the level of cholesterol in the blood and the excretion of creatine in the urine, as possible aids in early diagnosis and in gaging treatment with thyroid medication in the thyroid-deficient child.

BLOOD CHOLESTEROL

The work done at the Lahey Clinic with hypothyroidism and hyperthyroidism in adults indicated that the level of blood cholesterol might serve a useful purpose as a further laboratory check on the severity of hypothyroidism or hyperthyroidism, since the basal metabolic rate did not always give a true picture, and the clinical impression was difficult to define. A striking relationship between hypothyroidism, blood cholesterol, basal metabolic rate, and clinical improvement was observed. They concluded from

* Read at the Chicago meeting of the American College of Physicians, April 19, 1934.

their study that cholesterol reflected better the severity of hypothyroidism and the true clinical condition than does the basal metabolic rate.

We undertook an investigation for the purpose of determining the blood cholesterol relationship in thyroid-deficient children, having in mind the possibility of its use as a corroborating test in controlling thyroid dosage and maintaining metabolism at a normal level. In order to establish the average blood cholesterol for the group of hypothyroid children studied, the values of this lipid were determined in 25 children (table 1) ranging in age from two months to 11 years. In this group of patients, no derangement of cholesterol metabolism was present. The average level of blood cholesterol was 190 mg. per 100 c.c. of blood. This determination is consistent with the values found by other workers in this field as cited in the literature on blood cholesterol in infants and in older children.

TABLE I

Sex	Age	Cholesterol	Diagnosis
1. M.	2 mos.	200	Normal child
2. F.	2½ mos.	200	Normal child
3. F.	3 mos.	185	Pyloric spasm
4. F.	5 mos.	208	Normal child
5. M.	9 mos.	185	Upper resp. infection
6. M.	11 mos.	185	Cleft palate
7. F.	13 mos.	208	Pyelitis
8. M.	13 mos.	217	Achondroplasic dwarf
9. F.	14 mos.	200	Severe malnutrition
10. F.	15 mos.	147	Malnutrition, lues (?)
11. F.	2 yrs.	139	Tuberculosis (?)
12. M.	3½ yrs.	208	Mongolian idiot
13. M.	4 yrs.	167	Feeble-mindedness
14. F.	4½ yrs.	185	Eye affection
15. F.	5 yrs.	129	Eye affection
16. F.	5 yrs.	200	Eye affection
17. F.	5 yrs.	208	P. O. mastoidectomy
18. M.	5 yrs.	200	Malnutrition
19. F.	6 yrs.	192	P. O. herniotomy
20. M.	6 yrs.	192	Tonsillitis
21. M.	8 yrs.	200	Tbc. abscess chest wall
22. M.	9 yrs.	172	Observation for headache
23. M.	10 yrs.	217	Eneuresis
24. F.	11 yrs.	192	Obesity
25. M.	11 yrs.	217	Epilepsy

Originally eight boys and four girls were studied and the blood cholesterol values in these children when not under treatment ranged from 277 to 782. The presence of hypercholesteremia was definitely established in these twelve patients, and this excess of cholesterol in the blood was definitely reduced upon the administration of thyroid extract. Likewise, a marked clinical improvement followed.

Since the first communication, we have added to our list 12 more thyroid-deficient children, making a total of 24. In all of these hypercholesteremia was present when thyroid extract was not taken. In a number of the above, basal metabolism was impossible of performance and blood cholesterol was used as the guide in regulating therapy and following the clinical course.

I shall now present three patients in whom blood cholesterol was put to clinical use.

Case Reports

Case 1. G. M., a boy, aged 9½ years, had been under treatment previous to the undertaking of this study. It was not quite clear that he was a cretin, but after two months without treatment he presented typical characteristics.

On April 12, 1932 (up to which time he had been receiving from 2 to 3 grains (0.13 to 0.2 gm.) of thyroid a day), it was decided to stop thyroid. At this time his cholesterol was 156, the basal metabolic rate was plus 47, the pulse 94, and the weight 58¾ pounds (26.6 kg.). In the two months that thyroid was withheld, his weight rose to 65⅛ pounds (29.5 kg.), a gain of 6⅜ pounds. The cholesterol rose to 454, a change of 298 milligrams; the basal metabolic rate fell 58 points, and the pulse fell 40 points. When thyroid (2 grains daily) was started, the cholesterol fell to 172, a change of 282 milligrams, the basal metabolic rate rose 48 points, the pulse rose 42 points, and he lost 5⅞ pounds. After the two months without medication, the hair had grown coarse and the abdomen large, and myxedema had appeared.

Case 2. A. B., a boy aged 13, entered the hospital with a blood cholesterol of 454 and a basal metabolic rate of minus 41. The bony development of the wrist was that of a five year old child. In 15 days on approximately 1 grain (0.065 gm.) of thyroid extract daily, the cholesterol fell to 200 and the basal metabolic rate rose to 0.

At this time we were interested in the possibility of influencing cretins by other means, as for example, by insulin, as suggested by Chamberlain, since insulin will diminish the hypercholesteremia in diabetes. The pancreatic hormone was used for 43 days, during which period thyroid was stopped. The cholesterol rose from 200 to 454 and the basal metabolic rate fell from 0 to minus 35. When thyroid was again instituted, the cholesterol fell to 208, a fall of 246 points, and the basal metabolic rate gradually rose 71 points. In the course of a little over two weeks, the thyroid was rapidly increased from 1 to 8 grains (0.065 to 0.5 gm.) and the patient was kept on this large dose for a short period, following which improvement in his appearance and mental reaction took place.

Case 3. D.B., a girl 15 months old, is the youngest cretin in our group. She had a normal birth and was breast fed for three months. At three months, when breast feeding was stopped, the mother observed weakness of the child's voice, dryness of the skin and hair, and laziness in food taking and in movements. The infant was suspected of being a cretin. Basal metabolism was impossible since no enclosed respiratory chamber was available. Her initial cholesterol reading was 416 and upon thyroid therapy, starting with ½ grain and increasing to 1½ grains, marked clinical improvement was noted. The blood cholesterol fell gradually to 333, 312, 227 and the last few readings have been normal, 208, 179, and 147.

In this study the total blood cholesterol only was estimated. Cholesterol appears in the blood in the free state and as cholesterol ester, the relative proportions being 20 to 50 per cent of free cholesterol and 50 to 80 per cent of cholesterol ester. Schwartz and Topper suggest that the examination of the various fractions may be of further interest. They found in children with hypothyroidism not only an increase in the total blood cholesterol, but at times a disturbance of the ratio of ester to free cholesterol, of such a nature that the relative proportion is reversed; and they showed that this ratio may become normal after intensive treatment with thyroid extract. It is, therefore, possible that the determination of the ratio of free cholesterol to the ester may give us further valuable information in the diagnosis and treatment of hypothyroidism.

Creatine Excretion

The discovery of the metabolic functions of creatine in muscle metabolism has attracted considerable clinical interest to the study and treatment of disorders of the muscular system, particularly in pseudohypertrophic muscular dystrophy and in myasthenia gravis. Harris and Brand [1] have reviewed this subject well.

It seems likely that creatinuria in the human is related to defective creatine storage in muscle or to abnormally high creatine synthesis. Creatinuria occurs in all types of muscular dystrophy and in states of increased endogenous protein catabolism, as in fever and in certain cases of hyperthyroidism.

Normally creatine is not found in the urine of the male adult, but small amounts of creatine are excreted periodically in the urine of normal women. In infants and children, however, creatinuria is physiological in both sexes until about the age of puberty.

From the observations in current medical literature, it appeared that the relationship of the creatine metabolism to thyroid activity in children might be of clinical interest.

Extensive creatine and creatinine excretion studies were carried out on 34 children, including normals and children with various disease conditions. Detailed observations are reported at this time on two cases of hypothyroidism in children. Twenty-four hour urine specimens were collected on two female children with hypothyroidism, one (D. J., age 6 years) for 53 consecutive days, and another (V. K., age 11) for 36 consecutive days. The preformed creatine was determined by the Folin colorimetric method and the total creatinine by the Folin-Benedict method in duplicate. The patients were on a general hospital diet containing meat once a day and approximately a quart of milk a day. Rectal temperatures were taken three times a day.

These two cretins showed an absence of the physiological creatinuria of childhood when not receiving thyroid therapy or creatine by mouth. The absence of creatine from the urine was not due to a low protein intake as the diet described was not creatine free and contained an adequate amount of protein. In the case of the older subject (V. K.) the experimental period was started while she was still on thyroid extract. This patient showed a gradual decrease in urinary creatine as the amount of thyroid extract administered was reduced. She continued to excrete creatine for three days after thyroid therapy was discontinued.

The hypothyroid children studied have shown a definite change in creatine metabolism. This is characterized by a diminution or complete absence of the physiological creatinuria usually found in children up until the age of puberty. Thyroid feeding restores the hypothyroid child to the condition of creatinuria characteristic of the normal child. The creatinuria is seen to be a very delicate index of the effect of ingested thyroid inasmuch as it occurs even before any definite change is noted in the basal metabolism

and blood cholesterol. It is not possible to state how the thyroid hormone affects the creatine metabolism, but it is obvious that directly or indirectly it exerts a profound and determining influence upon the character of creatine metabolism. A probable explanation of the diminished creatine excretion is that it may be due to a low endogenous metabolism incident to hypothyroidism.

The comparison of the changes in creatine excretion with other criteria of the efficacy of treatment in hypothyroidism is interesting. It will be noted from the charts that following thyroid therapy a change in creatine excretion takes place long before there is a significant change in the basal metabolic rate, blood cholesterol, or body weight. From these observations, it seems apparent that measurement of the urinary creatine is a delicate index of the effect of thyroid administration. In view of the greater ease, simplicity, and reliability of creatine analysis than of the basal metabolic rate in children, it seems that this measurement may serve as a useful clinical aid in controlling thyroid medication.

Summary

The value of further aids in the diagnosis and treatment of thyroid-deficient children is discussed. The rôle that estimation of blood cholesterol and creatine excretion plays in the urine is indicated.

Blood Cholesterol. The blood cholesterol is high in children with untreated hypothyroidism, and is reduced by thyroid medication.

The level of blood cholesterol may be used as a guide to the efficacy of thyroid therapy.

Creatine Excretion in the Urine. The metabolism of creatine appears to be definitely influenced by thyroid activity during childhood.

During the period from infancy until about puberty, creatinuria is physiological. Hypofunction of the thyroid causes a decrease or complete cessation of creatine excretion which can be restored to normal values after the administration of thyroid extract. This is accompanied by a corresponding change in the clinical condition of the patient.

The creatinuria is a very delicate index of the effect of ingested thyroid inasmuch as it occurs before any definite change is noted in the basal metabolism and blood cholesterol.

From a comparison with other diagnostic criteria of hypothyroidism in children, the change in creatine metabolism appears to be an important finding which may be useful in diagnosis and in the control of therapy.

References

1. Harris, M. M., and Brand, E.: Metabolic and therapeutic studies in myopathies, with special reference to glycine administration, Jr. Am. Med. Assoc., 1933, ci, 1047–1052.
2. Bronstein, I. P.: Studies in cretinism and hypothyroidism in childhood; blood cholesterol, Jr. Am. Med. Assoc., 1933, c, 1661–1663.
3. Poncher, H. G., Visscher, M. B., and Woodward, H.: Creatine metabolism in children with hypothyroidism, Jr. Am. Med. Assoc., 1934, cii, 1132.

SEPTICEMIA *

By JOHN A. KOLMER, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

Definition. While the condition septicemia is well understood clinically yet it is hard to define in a clear and concise manner; hence many definitions have been offered. It is characterized by pronounced signs and symptoms of infection due largely to the presence of pathogenic organisms and their products in the blood and is usually associated with infection of the fixed tissues. In my opinion it is best defined as *an infection of the blood* because this phase greatly predominates in the clinical manifestations.

Emphasis is placed upon *infection* of the blood with all it implies as differentiated from invasion of this tissue. That is to say, the blood may be temporarily invaded by pathogenic organisms without showing any signs of infection; for this state the term *bacteremia* may be used. For example, streptococci may be found at times in the blood by culture in chronic arthritis without any signs or symptoms of infection as far as the blood is concerned. Furthermore it would appear that the gonococcus may be transmitted to the joints without clinical evidences of its temporary presence in the blood and it may be that the tubercle bacillus and other organisms may be found in the blood by culture without evidences of infection. All of this indicates that the mere presence of pathogenic organisms in the blood per se does not necessarily produce signs and symptoms of infection or constitute septicemia.

But when the immunological resistance of the blood is broken down by unusual numbers or virulence of the organisms or by other factors permitting the organisms to multiply in the blood along with the presence of toxins, aggressins or other bacterial agents, signs and symptoms of this infection of the blood are present and along with primary or secondary infection of the fixed tissues constitute the symptom complex or syndrome designated as septicemia.

In many instances this infection of the blood results in the production of abscesses or metastatic foci in other organs and tissues and especially in infections with the pyogenic cocci. When this happens the state is sometimes designated as *pyemia* or *septicopyemia* but it would appear that these terms are superfluous and unnecessary.

Since most instances of septicemia are secondary to infection of a fixed tissue some prefer to speak of the state as sepsis but this is hardly justified since it would appear that septicemia may sometimes occur without a detectable primary focus of infection or without pronounced evidences of infection

* Trimble lecture before the Medical and Chirurgical Faculty of Maryland, April 24, 1934.

at the probable portal of entry of the organism; this constitutes the so-called *cryptogenic septicemia* first described by Leube about 55 years ago.

Immunological Considerations. Our information on the mechanism of the natural and acquired defenses of the blood against infection is very incomplete but it would appear that whatever they may be they are inadequate, break down or fail to sufficiently develop in septicemia. Hence a very important phase of treatment consists in supporting, supplying or bolstering immunological resistance whenever possible and this sometimes requires the physician or surgeon to secure the coöperation of the expert bacteriologist and immunologist. To know what to do, when to do it and to meet the changing clinical conditions without the error of attempting to do too much requires unusual experience and common sense since all cases must be strictly individualized with hardly any two exactly alike; but more of this later.

Undoubtedly the blood is able to clear itself of small numbers of organisms by phagocytosis on the part of fixed cells of the reticulo-endothelial system in the liver, spleen, bone-marrow, lymph glands, etc. Indeed this phagocytosis would appear to be a very important factor in natural defense against septicemia and also in the mechanism of recovery, but apparently it requires the presence in the body fluids of adequate amounts of such antibodies as agglutinins and opsonins. In septicemia therefore the phagocytosis of organisms in the blood by reticulo-endothelium may fail or prove inadequate, not so much because the cells are "blocked," but because they are sickened by toxins or because there is insufficient production of these humoral antibodies, especially opsonins, believed to be so important in phagocytosis. These may be supplied to some extent by the timely administration of some of the immune sera in proper dosage or by the transfusion of blood from a normal or immunized donor.

Furthermore the blood naturally contains variable amounts of complement which appears to bear an important relationship to natural and acquired resistance against septicemia. Unfortunately its nature, the mechanism of its action and a knowledge of ways and means for causing its increase are but imperfectly understood. In septicemia it is usually decreased and this is an additional important reason for the transfusion of blood in treatment as a means of replenishment and increasing resistance.

In addition the blood naturally contains small and variable amounts of bactericidal antibody for most pathogenic organisms which may or may not produce lysis and may or may not require the presence of complement for bactericidal activity. For the want of a better term this substance is frequently spoken of as "protective antibody" and has been particularly identified with pneumococcus immunity and anti-pneumococcus serum. Unfortunately its source and the mechanism of its activity are likewise imperfectly known but it would appear to be a product of leukocytes and the cells of the reticulo-endothelial system. Its presence in whole blood or serum may be demonstrated in the test tube by the Cohen-Heist or other methods but better

in the living animal; in septicemia it appears to be exhausted. The transfusion of blood from a normal or immunized donor may furnish small amounts of this kind of antibody but larger amounts may be supplied in some of the antipneumococcus, antimeningococcus and antistreptococcus sera available for prophylactic and curative purposes.

Finally the blood may contain various natural antitoxins and it is a curious fact, to be referred to shortly in more detail, that septicemia rarely occurs in infection with diphtheria, tetanus and the bacilli of the anerobic gangrene group which owe most of their pathogenicity to the soluble or exogenous toxins. It may be that the antitoxic properties of the blood afford a large measure of protection but neutralization of toxins by transfusion of blood and the administration of immune sera exerts an important influence in the treatment of several of the septicemias and especially those caused by various types of hemolytic streptococci, the pneumococci and meningococci.

It is apparent therefore that the natural or acquired immunological principles of the blood and the fixed cells of the reticulo-endothelial system play a very important part in resistance to and recovery from septicemia, and that treatment of the state with appropriate immunological and supportive measures ranks next in importance to the carrying out, when possible, of surgical extirpation or drainage of infected areas of the fixed tissues along with attempts at disinfection with chemical agents.

Pathogenesis. In the great majority of cases of septicemia infection of the blood follows by way of the lymphatics or veins from local infection of the fixed tissues and in every case the first and most important phase of treatment consists of measures favoring the localization of the infection with prompt surgical extirpation or adequate drainage whenever possible. The primary focus, however, may be small and trivial with rapid infection of the blood when the infecting organism possesses unusual virulence and aggressiveness or when natural resistance is low, and surgical treatment requires the finest of judgment and skill since hasty operative measures may break down barriers and open avenues of extension of infection. And indeed septicemia may occur with practically no evidences of local infection at the portal of entry at all as, for example, in some cases of streptococcus, meningococcus, typhoid and anthrax septicemia. In my experience these septicemias, and especially those caused by the pyogenic cocci, invariably have the gravest prognosis, not only because it is impossible to institute local drainage, but because the absence of a well defined local lesion means the absence of a depot of local antibody production.

In the majority of cases, however, local infection of the fixed tissues occurs first with the production of lymphangitis and thrombo-phlebitis followed by invasion and infection of the blood with organisms or infected thrombi as immunological resistance is gradually or suddenly broken down. The resulting symptoms and secondary pathological changes in important organs are apparently due not so much to the organisms themselves in the

blood, as to the toxic substances they directly or indirectly produce; although the organisms as such, or in bits of thrombi, may produce embolic infections and abscesses in various organs and tissues of the body. It is for this reason that an eternal watch must be maintained for secondary infections in the course of all septicemias and especially those produced by streptococci, staphylococci, gonococci and colon bacilli with surgical drainage at the earliest favorable time whenever possible.

Bacteriological Considerations. While theoretically all pathogenic bacteria may produce septicemia yet some are especially likely and others especially unlikely to produce this state. The pyogenic organisms belong to the first group, especially streptococci, pneumococci, staphylococci and meningococci; and the toxin producing anerobes to the second. The order of frequency in which the various bacteria produce septicemia is, in my experience, as follows:

Hemolytic streptococci, especially *Streptococcus pyogenes*
Non-hemolytic streptococci, especially *Streptococcus viridans*
Pneumococci, especially in lobar pneumonia and sinusitis
Staphylococci, especially *Staphylococcus pyogenes aureus*
Bacillus typhosus
Meningococci
Gonococci
Bacillus anthracis
Bacillus coli
Spirillum recurrentis
Bacillus pyocyaneus

Among the rarer septicemias are those produced by:

Bacillus mucosus capsulatus
Bacillus influenzae
Bacillus proteus
Bacillus fecalis alkaligenes
Micrococcus tetragenes

Personally I have never seen septicemia due to the true diphtheria bacillus, although some cases are on record; nor to the tetanus and other bacilli of the anerobic gangrene group although this may be due in part to the infrequency with which anerobic methods of blood culture are employed. Doubtless *Spirocheta pallida* produces septicemia in the early stages of syphilis but it has never been cultivated from the blood although intratesticular injections of this tissue in rabbits have produced infection. Of course many of the protozoa and some of the metazoa as well occur in the blood but do not produce septicemia in the accepted meaning of the term.

In a broad and general manner there is a relationship between virulence of the organism on the one hand and septicemia on the other. That is to say, organisms possessing a high degree of invasiveness are especially likely

to produce the state. There is, however, such an important relationship between virulence on one hand and immunological resistance on the other that curious paradoxes are frequently seen. For example, the *Staphylococcus pyogenes albus* is usually regarded as an organism of low virulence leading a saphrophytic existence on the skin or mucous membranes and producing but small pimples and stitch abscesses; yet it can produce one of the most dangerous septicemias with which I am familiar. *Streptococcus viridans* is so low in virulence that it is almost impossible to kill a mouse or rabbit with it and yet what more mortal disease than its ulcerative endocarditis and associated septicemia? The anthrax bacillus produces little or no toxic substance at all and yet its septicemia with remarkably few symptoms ascribable to this state gives the disease its highest mortality. The diphtheria bacillus and even more the tetanus, botulinus and other anerobes of wound infections are terrible producers of exogenous toxins and yet how rarely do they produce septicemia. We need to know more about those bacterial poisons which are not particularly toxic of themselves but yet are capable of preventing or retarding phagocytosis and are commonly designated as aggressins and endotoxins, for an adequate understanding of the problems involved. Certainly inadequate or complete failure in phagocytosis and "walling off" at the portal of entry would appear to be an important factor in the production of septicemia.

General Etiological Considerations. Septicemia occurs at all ages and in both sexes but somewhat more frequently in the young and in the elderly; likewise more commonly among women than men on account of puerperal infections. More cases are seen during the colder months of the year because of the higher incidence of infections of the respiratory tract with special reference to sinusitis, otitis media, mastoiditis and pneumonia.

Diabetes mellitus, chronic alcoholism and chronic debilitating diseases are predisposing factors and particularly cardio-renal disease, arteriosclerosis, cirrhosis of the liver, cancer, Hodgkin's disease, etc., in relation to terminal infections with septicemia among elderly individuals. The site of primary infection or portal of entry, and the severity of the local infection at this point show great variation, in part dependent on the organism, ranging all the way from a severe puerperal endometritis to an insignificant blister on a toe from an ill-fitting shoe; and indeed, in some cases, there is no discoverable focus at all.

Hemolytic streptococci are by all odds the most frequent producers of septicemia and especially *Streptococcus pyogenes,* the usual or commoner portals of entry of these organisms being as follows:

1. Minute abrasions of the skin particularly in infections with the streptococcus of erysipelas.
2. Wounds and especially trivial puncture wounds or large lacerated ones resulting in lymphangitis.
3. Paronychiae, carbuncles, bed-sores and severe burns and, as a secondary infection, the pustules of small-pox.

4. Puerperal endometritis or sepsis where the chances for phlebitis are particularly marked.
5. Otitis media and mastoiditis and especially with lateral sinus thrombosis.
6. Sinusitis with special reference to the ethmoid and sphenoid cells.
7. Tonsillar infections secondary to scarlet fever, diphtheria and septic sore throat.
8. Osteomyelitis, especially in young persons.
9. Infected teeth and severe gingivitis.
10. The genito-urinary tract, especially after instrumentation, and an occasional case secondary to suppurative appendicitis, peritonitis, suppurative cholangitis, etc.

Streptococcus viridans septicemia is generally associated with ulcerative endocarditis with the portal of entry most frequently in the teeth, tonsils or sinuses.

Staphylococcus septicemia is fortunately much rarer but the primary foci are similar to those listed above for the streptococci with special reference to furunculosis, infected wounds, mastoiditis, osteomyelitis and puerperal endometritis.

Pneumococcus and *B. friedländer* septicemia are almost always secondary to infections of the respiratory tract and particularly lobar pneumonia, sinusitis, mastoiditis and bronchiectasis.

Gonococcus septicemia is fortunately rare but usually severe and fulminating with foci in the genito-urinary tract, joints or endocardium.

Meningococcus septicemia may occur as an acute fulminating infection through the mucosa and lymphatics of the naso-pharynx or as a late complication of meningitis.

Anthrax septicemia is nearly always secondary to primary infection of the skin (malignant pustule) or to infection of the bronchi and intestines.

In *typhoid fever* there is usually an initial bacteremia but a true septicemia may occur which is always of bad prognostic import if it appears late in the disease. *Bacillus coli* septicemia is not infrequent in conjunction with streptococci or staphylococci and especially as a terminal infection in cardio-renal and other chronic debilitating diseases or from primary foci in the biliary passages and peritoneum. *B. proteus* septicemia may also arise from infections of the urinary tract while *B. pyocyaneus* septicemia most frequently occurs in infants and young children producing rapidly fatal infections arising primarily from the gastrointestinal tract.

Pathological Considerations. Much may be stated about the gross and microscopic tissue changes in the various septicemias but with little advantage in such a general review of the subject as this aims to present.

Suffice it to state that the changes produced in any case are inflammatory or suppurative in character and generally consist of those found (1) at the site of initial infection or portal of entry; (2) secondary foci or abscesses in different organs or tissues; (3) proliferative changes in the bone-marrow,

spleen and other organs of the reticulo-endothelial system representing immunological response to the infection with blood regeneration and (4) degenerative lesions and especially cloudy swelling and fatty degeneration of the kidneys, liver, heart, brain and other organs generally ascribed to the effects of bacterial toxins.

As previously stated the tissue changes at the site of initial infection may be so slight as to readily escape detection. In my experience this has been particularly true of staphylococcus septicemia. I have seen such to be nothing more than a mere abrasion of the skin with almost complete healing at the time of a rapidly fatal septicemia, and as these lines are written I have an unusually severe case following a small and healed furuncle of the skin of a finger. In meningococcus septicemia the initial lesion may be nothing more than a moderately severe naso-pharyngitis without suppuration, but as a general rule the initial lesion of most septicemias, and especially of those caused by streptococci, show pronounced suppurative changes with septic phlebitis and lymphangitis as, for example, those occurring in mastoiditis, endometritis, etc.

The secondary foci are usually embolic in character and show many curious and unexplainable distributions in the different septicemias, involving in some instances the selective affinity of organisms for certain tissues. For example, the meningococcus localizes mainly in the meninges, the gonococcus in the muscle sheaths, periosteum of the long bones, peri-articular tissues and lungs, etc. But metastatic or embolic abscesses may occur almost anywhere; in particular they are apt to affect the kidneys, lungs, pleurae, brain, spleen and endocardium. Septic or embolic bronchopneumonia and pleuritis are always to be feared, and especially so in staphylococcus and streptococcus infections.

As a general rule the spleen is enlarged, if the patient lives long enough, and is either of the soft red type showing marked hyperplasia and phagocytic activity of the reticulo-endothelial macrophages with acute congestion of the pulp, or of the grey type with a great increase of the pulp cells and large numbers of oxidase-containing myeloid elements. The bone-marrow is apt to be opaque because of a great increase of myelocytes in response to the need for granulocytes and especially for neutrophiles for combatting the infection and shows evidences of erythroblastic activity stimulated by the effects of blood destruction.

Sooner or later, depending upon the severity of the infection, the toxins and the pyrexia are apt to produce hyperemia with cloudy swelling and fatty changes especially in the heart, liver, kidneys, and adrenal glands, etc. Acute meningeal congestion, or so-called toxic meningismus with hyperplasia of the arteriolar endothelium may be observed, and is responsible for the mental symptoms of headache, delirium and coma which are so likely to be present. The much dreaded paralytic ileus I believe is due to involvement of the posterior lobe of the pituitary gland. It is expressed clinically by initial diarrhea with terminal abdominal distention, nausea and vomiting.

Laboratory Aids in Diagnosis. This naturally brings one to a consideration of laboratory aids in the diagnosis of septicemia, especially, since this is essentially a bacteriological problem, with reference to study of the primary focus and blood cultures.

Altogether too frequently the bacteriological examination of the primary or initial foci of infection by smears and cultures is overlooked and when septicemia is finally suspected clinically much valuable information is lacking. Furthermore the chances of developing septicemia may be sometimes estimated by a knowledge of the nature of the initial infection. For example septicemia following staphylococcus mastoiditis is rare as compared with streptococcus infections with or without lateral sinus thrombosis; streptococcus endometritis is far more likely to produce septicemia than staphylococcus or other infections and in lobar pneumonia pneumococci of group IV are less likely to produce septicemia than types I, II and III although probably the group IV septicemia is even more dangerous when it does occur.

Without doubt blood cultures are of primary importance provided the proper technic is employed. Indeed septicemia is sometimes first detected by them, and the absence of classical signs and symptoms by no means excludes the possibility of a blood stream infection. As the presence of bacteria in the blood may be intermittent, two or more cultures at intervals of one or two days may be required. As a general rule microörganisms develop rapidly in blood cultures in septicemia but all should be kept under observation for at least five to ten days before reporting sterile results.

Great care is required in taking the blood to guard against contamination with staphylococci (particularly *Staphylococcus albus*) and streptococci (particularly non-hemolytic types) from the skin. Indeed it is usually advisable to repeat the culture at least once before arriving at the diagnosis of a staphylococcus septicemia in order to guard against error due to contamination.

As shown by Ottenberg, there is an advantage in taking blood for culture from a vein draining an infected area whenever this is possible. Cultures of blood from the internal jugular veins of individuals with suspected lateral sinus thrombosis in mastoiditis have, for example, sometimes yielded positive results when cultures from veins at the elbow were sterile or have shown a smaller number of bacteria. In his opinion the finding of a much greater number of bacteria in the blood from one internal jugular vein than from the other confirms the diagnosis of lateral sinus thrombosis although it is impossible from the count alone to tell on which side the thrombosis is located.

As a general rule it is a good practice to culture relatively large amounts of blood like 5 to 10 c.c., and I have found glucose hormone broth with a pH of about 7.4 to 7.6 quite suitable in 100 to 200 c.c. amounts. By plating measured amounts of blood like 5 c.c. with 10 c.c. of glucose hormone agar, an idea of the numbers of bacteria per cubic centimeter may be obtained which is of value in estimating the gravity of the infection as well as being a guide in evaluating the results of treatment.

Unfortunately we do not have available at present a practical method for detecting or measuring the amounts of bacterial toxins which are commonly believed to be present in the blood in septicemia. It is likely that skin tests employing the serum of the patient injected intracutaneously in the lower animals and especially the rabbit, may be of aid in this connection, but mice, rats, guinea pigs, and rabbits possess such a high natural immunity to staphylococci and streptococci, that I, at least, have not been able so far to work out an acceptable method by intraperitoneal and intravenous injections of serum.

In this connection I may also mention that it is sometimes of value to *estimate the bactericidal and bacteriostatic activity of the blood* to determine at the outset the patient's chances of developing septicemia. This is done after a method of Cohen consisting in placing a small amount of pus or culture in the bottom of a sterile test tube and adding 5 c.c. of blood. If organisms develop in this whole coagulated blood, it may indicate a breakdown of immunologic resistance and the possibility of the development of a blood stream infection. If organisms do not develop, the reverse may be true, although I have seen septicemia develop under such conditions apparently as the result of a subsequent reduction in immunologic resistance.

Total and differential leukocyte counts are of course well known and appreciated in the diagnosis of septicemia and should be made at frequent intervals as a guide to the severity and progress of infection. A leukocytosis due largely to an absolute increase of polymorphonuclears along with a relative or absolute decrease of eosinophiles has long been accepted as the typical change.

But an estimation of the metamyelocytes or immature polymorphonuclears greatly improves the value of the differential leukocyte count in diagnosis and also as a means of estimating the severity and progress of septicemia. These cells are readily detected and divided into two types, the young and the old or banded forms. In the usual differential count they have been included in the percentage of large lymphocytes, transitionals and polymorphonuclears and their significance entirely lost. By the newer method, however, it is possible to obtain valuable information even when the percentage of polymorphonuclears is about normal.

Normally the blood contains none of the young metamyelocytes and about 4 per cent of the older ones. In acute infections both are increased and designated by Schilling as a " shift to the left." This shift may occur with but a slight and insignificant increase of the polymorphonuclears. By dividing the number of polymorphonuclears by the number of metamyelocytes, my colleagues, Boerner and Gerard, have worked out the " nuclear index " as a means of reporting. For example, there are normally about 4 metamyelocytes to 60 polymorphonuclears giving an index of 15. If the metamyelocytes increase, the index becomes lower so that an index of 10 to 15 constitutes a slight shift to the left, 5 to 10 a moderate shift, and below 5 a marked shift. *I strongly advise the adoption of this shift to the left*

and nuclear index method for routine differential leukocyte counts and reports.

Furthermore, as shown by Boerner it is advisable to abolish the usual custom of reporting the different leukocytes by percentages since it is possible for the polymorphonuclears and other types to be present in a normal percentage while being actually increased. It is much better to report the actual number of each variety per cu. mm. of blood, the normal for older children and adults being as follows:

Lymphocytes	1000 to 3000
Monocytes	100 to 600
Polymorphonuclears	3000 to 7000
Eosinophiles	50 to 400
Basophiles	0 to 50

This is a more accurate and useful method since it gives the " absolute " number of the different leukocytes, as one or more types may show important changes which are not revealed by the usual percentage or " relative " system. In septicemia particular interest is attached to the polymorphonuclears and eosinophiles and I recommend the adoption of this plan even though it entails the task of forgetting percentages and training the mind to interpret the results on the basis of the total numbers of the different leukocytes per cubic millimeter of blood.

Urine examinations are of course required with special reference to specific gravity as an index of fluid intake and output, and to albumin as an index of tubular changes. The presence of leukocytes and erythrocytes may be an index of focal glomerulo-nephritis which is likely to occur, especially in streptococcus infections. Finally bacteriological examination of catheterized specimens is indicated when embolic abscesses or pyelo-nephritis are suspected.

In this connection mention may also be made of the value of *blood chemical determinations:* urea nitrogen as an index of functional capacity of the kidneys; glucose in relation to diabetes mellitus which predisposes to septicemia and always entails an especially poor prognosis; and cholesterol which when high unfavorably influences resistance probably because of associated involvement of the adrenal glands.

And finally an *examination of the cerebrospinal fluid* is of course an invaluable aid when meningitis is suspected. The usual findings, however, are typical of the acute meningeal congestion or so-called " serous meningitis " of septicemia, i.e. a perfectly clear fluid under increased pressure with normal total cell count, with no increase of protein or decrease of sugar and bacteriologically sterile.

Symptomatology and Clinical Diagnosis. My records cover 282 cases of septicemia seen in hospital and consultation practice during the past 20 years, yet it is difficult and almost impossible to present a brief account of the clinical manifestations. Indeed it seems to me that no two cases caused even by the same kind of organism are ever exactly alike and this is not to be wondered at when one remembers the possible variations due to the kind and

virulence of infection on the one hand with the age and immunological resistance of infected individuals on the other, not to mention the presence or absence of predisposing factors, the site and severity of initial infection, the distribution and severity of complications and what not.

Suffice it to state that some septicemias are fulminating when virulence is extremely high or resistance extremely low, with death in a few days. The majority, however, are of the ordinary acute type running a course of one to several weeks; while a few are of the subacute or chronic type in which the septicemia or positive blood cultures may persist for many weeks and even several months with surprisingly few clinical manifestations until the terminal stage is reached—with death, as always happens in *Streptococcus viridans* endocarditis, or recovery, as sometimes occurs and especially in the streptococcus septicemia following abortion, childbirth or surgical infections.

One thing is certain, namely, that on the one hand, without blood stream infection, enough toxins may be absorbed from a severe primary focus to closely mimic the clinical picture of septicemia and that, on the other, septicemia may exist with so few of the classical symptoms as to make a positive blood culture a matter of surprise. In other words an actual finding of organisms in the blood by one or more cultures is the criterion in the final analysis and reliance cannot always be placed on symptoms alone in diagnosis.

Furthermore the *incubation period* may vary apparently from a few hours or days to several weeks. Here again virulence of infection and resistance are the determining factors. For example during epidemics of meningococcus meningitis with high virulence of the organism, healthy individuals have succumbed to the septicemia within a few days of the time of infection and before the onset of meningitis, while it is not unusual for streptococcus septicemia to develop one or more weeks after mastoidectomy; not to mention the weeks that may elapse between the infection of teeth or tonsils and the development of subacute streptococcus endocarditis with septicemia. No two cases are ever exactly alike and it is impossible to assign even approximate periods of primary incubation for the different septicemias.

Probably the most constant and characteristic clinical manifestation is the high continuous or intermittent " steeple chase " type of fever reaching its low point in the morning and peak late in the afternoon or evening. A few days of this sort of thing is usually sufficient to suggest the possibility of septicemia by a mere glance at the graphic record and especially when the fever is accompanied by chills or chilliness, a rapid bounding pulse, increased respirations, flushing of the skin with profuse sweats, a dry and tremulous tongue with thirst and sometimes unusual mental excitement or delirium soon to be followed by apathy and a comatose state.

Add to these some nausea with or without vomiting; constipation or often times a looseness of the bowels followed in a few days by gaseous distention of the intestines which may become extreme when the ileus is severe and always of bad prognostic import; various erythematous, vesicular or petechial exanthems, especially in streptococcus infections; muscular and

arthritic pains, especially in staphylococcus septicemia; the signs and symptoms accompanying the primary focus of infection; and the picture is usually complete.

In the meantime there is present a sharp leukocytosis with a shift to the left, an increasing anemia with a sallow or icteroid discoloration of the skin, especially in staphylococcus and streptococcus infections; slight enlargement of the spleen and sometimes of the liver if jaundice has developed; scanty, high colored and albuminous urine and a blood culture usually positive after a day or so of incubation. Not infrequently some cyanosis is present with crepitant râles to be heard posteriorly at the bases of the lungs. Septic bronchopneumonia with pleuritis may develop. Likewise metastatic or embolic abscesses may occur in the kidneys and other organs, especially in staphylococcus septicemia, with abscesses in muscle sheaths about the shoulders, arms, legs and various joints, and with the production of periostitis and osteomyelitis. Eternal vigilance and daily examination of the patient are required because abscesses come on like a thief in the night with surprisingly few of the classical signs of dolor, calor and rubor, and they require early detection and adequate drainage.

Another thing is always certain, namely, that as long as blood cultures are positive there is some focus or foci of infection of the fixed tissues constantly feeding organisms and toxic substances into the blood so that surgical drainage is frequently of great importance in treatment whenever possible, not only of the primary focus but of secondary foci as well. Following recovery abscesses may continue to develop over months of time and especially abscesses of the muscles and bones in staphylococcus infections.

Treatment. I am convinced that the treatment of septicemia will never be on a completely satisfactory basis until there is available a chemical agent or agents capable of bringing about the disinfection of the fixed tissues and blood when administered in nontoxic amounts by intravenous or intramuscular injection. Such an agent must be comparable in curative effects to the organic arsenicals like arsphenamine and neoarsphenamine in the treatment of syphilis and of other spirochetal infections. In other words I believe that chemotherapeutic research with the hope of evolving such compounds is urgently required; certainly there are no such compounds available at present although a few, to be mentioned shortly, are not without some beneficial effects. Furthermore serum therapy has not solved the problem of treatment and the general result has been that a great number of various drugs, sera and plans of treatment have been advocated with none to be particularly recommended. Space does not permit a detailed review of the enormous literature on this subject and I must content myself with a brief statement of those therapeutic procedures which I have found helpful, all of which are based upon the fundamental principles influencing infection and immunological resistance previously discussed.

In the first place adequate surgical drainage of the primary and secondary foci of infection of the fixed tissues is in my opinion of fundamental im-

portance and especially in the so-called surgical septicemias so frequently caused by hemolytic streptococci and staphylococci. This requires the very finest of surgical judgment and skill because hasty and too extensive operative measures may be meddlesome and open up new channels of infection on the one hand, while overlooking a focus or providing inadequate drainage may be disastrous on the other. On the whole, however, I believe that free drainage is the correct principle and that it is better to err on the side of too many exploratory incisions than too few. Furthermore the surgical dressings applied to accessible foci should be such as to promote the best possible drainage and in this connection I have learned to prefer hot moist dressings of hypertonic saline solution (10 per cent) or equal parts of 20 per cent saline and saturated boric acid solutions.

In hemolytic streptococcus infections I still believe in the early administration of antistreptococcus serum in adequate dosage. I doubt if such sera are bactericidal but they may contain helpful amounts of agglutinins and opsonins for the promotion of phagocytosis and likewise helpful amounts of antitoxin. A common mistake is to delay administration too long or to give too small doses. My advice is to administer serum very promptly by intravenous or intramuscular injection every 12 to 24 hours for at least four to six doses, the amount varying according as to whether concentrated or whole serum is employed, the dosage of the latter being about 30 c.c. by intramuscular and 50 to 100 c.c. by intravenous injection. There may be an advantage in testing several sera for their agglutinating titers for the streptococci secured in cultures and employing that which shows the highest titer, although the agglutinating power of a serum is not an exact measure of its efficacy, nor does the absence of agglutinins necessarily indicate that such a serum is without specific and nonspecific therapeutic value. In hemolytic streptococcus septicemias intramuscular injections of scarlet-fever antitoxin have also been used with alleged success. I have used it in seven cases of otitic origin with lateral sinus thrombosis; there were no unfavorable reactions and I gathered the clinical impression that the serum may have been of value in lessening the degree of toxemia since five of these patients recovered. In staphylococcus septicemia serum should also be administered if procurable while in pneumococcus infections due to types I and II, meningococcus, gonococcus and anthrax septicemias the prompt and free administration of the respective immune sera should be resorted to at the earliest possible moment.

Of course the necessary precautions should be observed especially when serum is given by intravenous injection. Adrenalin chloride 1 : 1000 is usually an effective antidote for immediate reactions when given subcutaneously or intramuscularly in dosage of 0.5 to 1.0 c.c. and should always be in readiness. Preliminary skin tests for allergic sensitiveness are always advisable and especially before intravenous injections. The intracutaneous test consisting of the injection of 0.2 c.c. of a 1 : 10 dilution of serum is usually employed and I generally inject the serum selected for treatment

rather than normal horse serum. A conjunctival test consisting in placing a drop or two of 1 : 10 dilution of serum into one of the eyes is also employed but at this writing I am not able to express an opinion of its relative sensitivity and practical value. If either or both of these tests yield positive reactions an injection of serum should be given with special precautions, but I do not give a horse immune serum at all in any amount or by any route or method to asthmatics giving positive skin or eye reactions to such serum.

Furthermore I believe that blood transfusions are usually helpful, especially in the treatment of streptococcus and staphylococcus septicemias. It is sometimes stated that they may be harmful but I have never seen evidence of this in my experience. Personally I believe that they are always indicated and frequent small ones appear more helpful than occasional large ones. My practice is to give adults about 250 c.c. every three or four days for the purpose of replenishing complement and natural bactericidal and opsonizing principles as well as healthy leukocytes. When anemia is present, as it usually is in the later stages, they may be likewise helpful in combatting anoxemia by furnishing erythrocytes and hemoglobin. I have learned to prefer a direct method but the method chosen should be that with which the physician is most familiar as transfusion reactions should be avoided as much as possible and especially in very sick individuals.

In this connection it is always advisable to employ direct matching tests. Donors may be selected belonging to the same group as the patient but if time and facilities permit, the final selection of a donor should rest upon direct tests in order to avoid the regrettable error of using a donor of a subgroup. This is particularly true of Group A donors (corresponding to Group II of Moss and Jansky). I also strongly recommend in the interests of safety and simplicity dropping the Moss and Jansky classifications and employing only that of Landsteiner:

Landsteiner Group A, corresponding to II of Moss and II of Jansky
Landsteiner Group B, corresponding to III of Moss and III of Jansky
Landsteiner Group AB, corresponding to I of Moss and IV of Jansky
Landsteiner Group O, corresponding to IV of Moss and I of Jansky

Without doubt blood transfusion is a valuable part of the treatment of septicemia not only for the purpose of supplying fresh leukocytes for the elaboration of bactericidal substances if the patient's leukocytes are exhausted and incapable of immunologic response, but also for the purpose of supplying the patient with complement, as his own is likely to be reduced below normal levels.

In this connection the relative value of plain and " immunotransfusions " is commanding considerable attention but despite the fact that I have used both for many years I am as yet unable to express an opinion of value on their relative merits. The latter term was used first by Sir Almroth Wright for a method consisting of adding a quantity of vaccine, like 1,000,000,000 stock staphylococcus vaccine to about 500 c.c. of defibrinated blood

from a compatible donor; after waiting for about an hour the mixture was given the patient intravenously. According to Wright this procedure results in an elaboration of nonspecific bactericidal substances from the leukocytes of the donor's blood effective upon all ordinary pathogenic bacteria and not only upon the organism with which the blood had been vaccinated.

In my experience it was found that this method of "vaccinating blood in vitro" results in an increase of bactericidal activity but intravenous injections were usually followed by rather sharp reactions which I thought were caused by the bacterial protein. The therapeutic effects were due in my opinion at least in part to this nonspecific bacterial protein reaction.

Later, Colebrook and Storer suggested a method for determining whether an individual patient ought to be treated by immunotransfusion by testing the phagocytic activities of the leukocytes. If the phagocytic intake is one-third or less than that obtained with a normal blood, immunotransfusion is to be employed by the following method:

A compatible donor is given a subcutaneous injection of 1000 million stock staphylococcus vaccine and his blood used four or five hours later. Colebrook and Storer advised the use of defibrinated and not citrated blood. I have employed the method with apparent success by using direct methods of transfusion. I observed less reaction in patients and there was no danger of bacterial contamination of the blood.

Still later Hooker, Dick and others employed donors previously immunized with a vaccine prepared with the infecting organism of the individual patient. Their technic consisted in general terms of the subcutaneous injection of 500 million, 1000 million and 2000 million heat-killed bacteria on successive days followed by transfusion about one week later.

One drawback to this method is the time required for the immunization of the donor although I have found the method particularly applicable to the treatment of those cases of staphylococcus and streptococcus septicemia surviving the acute stage and requiring transfusions later on. In all instances of these septicemias it is my practice, therefore, to secure one or two compatible donors as soon as possible and start their vaccination in order to have them in readiness in from 10 to 14 days if transfusions are required as is generally the case.

At this writing, however, I am more impressed with the probable value of a method of nonspecific immunotransfusion advocated by Brody and Stephenson consisting in giving a compatible donor 50 to 75 million *B. typhosus* vaccine by intravenous injection. This usually produces a reaction of chills, fever and leukocytosis in about an hour and the blood is used three to seven hours later after the acute reaction has subsided. One drawback to the method is the unpleasant reaction in the donor requiring him to go to bed and it is therefore objectionable to professional donors. I have seen results, however, which gave me the impression that the method may be superior to plain transfusions.

Finally, since sera for streptococcus septicemia may not contain anti-

bodies for a particular strain and as antistaphylococcus serum may not be available at all, Cadham has sought to develop a method for preparing autogenous sera and administering these in conjunction with normal serum from compatible donors to furnish the complement deficiency so frequently observed in septicemia.

The method adopted was as follows: "The invading microörganism was obtained from blood cultures and grown in serum-glucose broth. The resulting growth having been centrifuged three times in normal saline, a vaccine, in which the microörganisms had been heat-killed at the minimum lethal temperature, was then prepared and inoculated into rabbits and guinea pigs. These animals tolerate comparatively large doses of a vaccine containing either streptococci or staphylococci, especially if the organisms are washed free of the media. The dose of the vaccine, starting with one-quarter billion and working up to three billion organisms, was given on alternate days. An agglutination titer of one to five thousand may be obtained as early as the sixth day. Any time after the fifth day blood was drawn from the heart with aseptic precautions and without causing the death of the animal. This blood was placed in the ice chest for eight hours, and then the serum was pipetted off. The patient was inoculated subcutaneously with from 3 to 4 c.c. of this serum. Twelve patients were treated with rabbit serum, and six with guinea pig serum. There seems to have been no appreciable difference in the results obtained.

"A donor whose blood was completely compatible with that of the patient was obtained as soon as possible. The donor reported at the laboratory and from 50 to 60 c.c. of blood were withdrawn in large vacuum tubes. This was left at room temperature for 15 minutes and then placed in the ice chest for 15 hours. The serum was next pipetted off with all aseptic precautions, examined for sterility, diluted with equal parts of saline, and given by means of a syringe to the patient intravenously. Thus, the patient received an inoculation of the animal serum containing the antibodies subcutaneously, and also received a transfusion of from 25 to 30 c.c. of the donor's serum containing complement. Originally, the treatments were given one week apart, but this was subsequently shortened to two day intervals. Treatment was continued until negative blood cultures were obtained and the patient showed considerable improvement. The greatest number of treatments given to any one patient was seven.

"To isolate the infective organism, culture it, inoculate the animal with the vaccine, and to await the development of amboceptors of value, required at least five days; and to obtain a serum with a more powerful agglutination titer, 12 days. Frequently, the emergency of the case did not permit any such delay. To overcome this difficulty some rabbits and guinea pigs were inoculated with various strains of streptococci and staphylococci. Certain animals received inoculations of a vaccine prepared from 15 strains of streptococci, which had been obtained from as many different cases of local

or general sepsis. Patients were treated at once with the serum from these animals, pending the development in other animals of a specific serum."

From the standpoint of biologic therapy reference may be also made to the probable value of *bacteriophage* in the treatment of staphylococcus septicemia provided a virulent strain is available known to be highly lytic by actual laboratory test for the organism recovered from the blood. Unfortunately it is much more difficult to secure virulent bacteriophage for hemolytic streptococci and still more so for non-hemolytic strains with special reference to *Streptococcus viridans*. If bacteriophage is available I am prepared to recommend its use, especially in the treatment of staphylococcus infections. The dose may be 5 c.c. subcutaneously once a day or better 1 to 2 c.c. by intravenous injection once or twice a day. Reactions by the latter route sometimes occur but are not harmful and apparently helpful if not too severe.

Indeed I am convinced that so-called *non-specific protein reactions* are sometimes very helpful in the treatment of the septicemias, particularly if given early while the bone-marrow and other tissues of the reticulo-endothelial system have the capacity for favorable reactions. The intravenous injection of bacteriophage may have this side effect or the intravenous injection of 50 to 100 million dead typhoid bacilli may be substituted. If an autogenous vaccine has been prepared it may be used instead in doses of 25 to 50 million by intravenous injection. Otherwise one may try the intramuscular injection of 5 to 10 c.c. of sterilized milk but in my experience the intravenous injection of vaccine has been apparently more helpful. It is to be emphasized, however, that such agents are only to be recommended and safely used in the very early stages of septicemia and not at all in the latter stages when the patient is greatly debilitated, nor in the presence of chronic myocarditis in elderly individuals.

In this connection reference may also be made to the production of sterile abscesses by the intramuscular injection of 1 c.c. of turpentine diluted with 3 c.c. of sterile olive oil, especially in the treatment of those occasional cases of cryptogenic staphylococcus and streptococcus septicemia without discoverable primary or secondary localizations.

In addition to these measures of surgical drainage and biologic therapy recourse may be had to the intravenous injection of various chemical agents and so many have been advocated that it is at once apparent that no one of them is satisfactory. In my experience they have sometimes apparently aided in reducing the degree of septicemia but none that I know of are capable of sterilizing the fixed tissue infections which are of such fundamental importance as foci of toxin production and constant feeders of organisms into the blood. In streptococcus septicemia, particularly that of puerperal origin, I have sometimes thought that the intravenous injection of neoarsphenamine or sulpharsphenamine was helpful as suggested by Colebrook of London. The dose of either may be 0.3 to 0.45 gm. dissolved in 20 to 30 c.c of sterile water and slowly injected every three or four days.

Pregl's solution of iodine (concentrated) may also be tried in staphylococcus and streptococcus septicemia, the adult dose being 20 c.c. by intravenous injection every 24 or 48 hours. It has the advantage of low toxicity and may be safely given even in the presence of focal glomerulo-nephritis.

Rivanol in dose of 40 c.c. of 1 : 1000 solution by intravenous injection is also sometimes helpful but hardly more so than similar doses of 0.5 per cent solutions of neutral acriflavin. In my experience gentian violet in doses of 30 to 40 c.c. of 0.5 per cent solution by intravenous injection has not been as successful as indicated by the reports of others. However, it may be worthy of trial especially in staphylococcus septicemia but one must be sure to use the purified product prepared for intravenous injection.

The mercurial compounds must be used with caution in the presence of evidences of nephritis. I have not had the encouraging success with mercurochrome reported by many in the literature. But I still believe it may be worthy of trial in selected cases, especially in staphylococcus and *B. coli* septicemias. The ordinary adult dose may be about 25 c.c. of a freshly prepared 1 per cent solution by intravenous injection or one may give 5 to 10 c.c. at daily intervals since a reaction does not appear necessary for therapeutic effects although in my experience best results have apparently occurred when reactions of chill, fever and leukocytosis were induced. Metaphen in dose of 20 c.c. of 1 : 1000 is much safer, produces little or no reaction and on the whole seems to be about as helpful as mercurochrome.

In addition to such biologic and chemotherapeutic treatment other measures are of great importance. Among these is to be mentioned the advisability of keeping the fluid intake to at least 3000 c.c. per day for adult cases and the daily intravenous injection of glucose, the average dose being 25 to 50 c.c. of a sterile 50 per cent buffered solution by slow injection. In some instances the continuous slow intravenous injection (*venoclysis*) of 10 per cent glucose or Ringer's solution is advisable as recommended by Hendon at the rate of no more than 200 c.c. per hour with interruptions in order not to exceed 3000 to 4000 c.c. per day. The urine should be examined at frequent intervals and the injection of glucose stopped when there is 1 per cent or more glucose present. During the height of the fever sponging with cool water is usually helpful and does much to allay mental confusion and delirium.

In the meantime the *diet* should be largely of milk, fruit juices, broths and soft foods with an attempt to furnish vitamin A and to maintain a high daily caloric intake.

It is also my custom to give one to two ounces of whiskey or brandy each day in divided doses preferably in the form of eggnogs. Strychnine is also sometimes of service in doses of 1/30 grain two or three times a day and digitalis is occasionally required. In the presence of much pain and restlessness I do not hesitate to give pantapon and even morphine sulphate by subcutaneous injection although the latter must be used with caution if there is much distention or any nausea. Cathartics are not usually required as

daily enemas usually suffice and if there is distention these may be of 1 per cent solutions of sodium bicarbonate or about a pint of equal parts of milk and molasses at a comfortable hot temperature. Ileus is always to be feared and may be treated by such measures along with turpentine stupes for an hour and repeated every three hours along with the subcutaneous injection of 0.5 to 1.0 c.c. of surgical pituitrin every three or four hours as required. Oxygen should be given if cyanosis develops and particularly by means of a tent.

With all such measures to be considered it is easy to over-do treatment and deny the patient the greatly needed *rest* in a quiet and cool room. Indeed it is not unusual for treatment to be meddlesome in these regards and every case should have a daily therapeutic program arranged to provide the maximum of rest for the patient. It is almost impossible to foretell events and arrange treatment very far in advance; rather it must usually be arranged day by day according to individual conditions and requirements. The temperature, blood cultures and leukocyte counts are usually the best guides and blood cultures should be made every day or two whenever venapuncture is done for transfusions, the injection of glucose or chemical agents, etc.

Prophylaxis. With so much to be considered in the treatment of the septicemias, especially those caused by staphylococci and streptococci, it is apparent that the methods proposed from time to time very nearly exhaust human ingenuity on this subject but yet the efficiency of a doctor in any particular case is in inverse ratio to the diversity of his armamentarium. In time, we must believe, neutralizing sera of greater efficacy will be produced; and in spite of disappointments so far, Ehrlich's " therapeuticum magnum," the intravenous drug of universal adaptation, will be discovered. But until then the need for preventive or prophylactic measures against septicemia will persist and in this connection it may be stated that a weapon of value, namely, the prophylactic use of antistreptococcus sera, is in our hands today but is not being used as frequently as should be the case.

Why should the use of antistreptococcus serum be so often delayed until severe infection is established? The immune sera are primarily prophylactics; they do not cure damaged tissues but protect those still unaffected. Furthermore their efficacy is directly related to the rapidity with which toxins are absorbed and in streptococcus infections absorption is unusually rapid. The essential is to use the serum early. If it is a good routine practice to inject antitetanic and antigangrene sera for prophylactic purposes in street accidents, although the risks of tetanus and gangrene are comparatively slight, it should be just as much a routine to administer antitoxic streptococcus serum in all cases of abnormal labor and abortion in which the incidence of puerperal sepsis is high as well as in wounds at operations on septic cases, after mastoid operations and, in fact, to any deep cut inflicted with a dirty instrument, needle pricks at postmortem examinations, etc. Little in immunology is so certain on the basis of animal experiments,

as the usefulness of such sera when given prophylactically—and their comparative uselessness when infection is well established. Neither the surgeon nor the obstetrician appears to have as yet learned these lessons. It is highly probable that the administration of such sera before or after every difficult labor and abortion would reduce the incidence and mortality of streptococcus septicemia. It is true that the patient may be made serum-sensitive but there is not the slightest reason why antisera should not be made from animals other than the horse, and in this way overcome the difficulty.

I plead therefore for the wider use of intramuscular injections of antistreptococcus serum for prophylactic purposes and especially in puerperal and surgical cases. The dose may be 10 to 40 c.c. according to whether whole or concentrated sera are employed and two or three doses at three day intervals are advised.

Furthermore if septicemia is truly an infection of the blood due primarily to a complete local breakdown of barriers at the primary focus, as I believe is the case in most instances, is it not apparent that we are sometimes insufficiently drastic in surgical treatment? At first sight multiple incisions or even amputation of an arm may not seem justifiable merely for a cut finger followed by septicemia; but the price is worth paying if it is the only means of saving life. In other words a policy of undue delay in resorting to prompt and even drastic measures may result in disaster and especially in relation to prompt surgical drainage when possible and the early administration of immune sera in adequate dosage.

THE UNITED STATES PHARMACOPOEIA XI:

ITS RELATION TO INTERNAL MEDICINE AND THE SCIENTIFIC NATURE OF ITS REVISION *

By VIRGIL E. SIMPSON, A.B., M.D., F.A.C.P., *Louisville, Kentucky*

SCOPE

What Should the Pharmacopoeia Contain? One of the functions of the Revision Committee is to admit into the Pharmacopoeia a carefully selected list of medicinal substances of known origin, possessing therapeutic usefulness. This object differs in no essential detail from that enjoined on the Revision Committee of the first edition published 114 years ago, which stated that the object was "to select from among substances which possess a medicinal power, those, the utility of which is most fully established and best understood." In each edition from that first one to the one now undergoing revision the principle of a carefully selected list of therapeutically useful medicines has guided each succeeding Revision Committee in fixing the boundaries of its scope.

The members of the Revision Committee derive from both the medical and pharmaceutical professions; the present Revision Committee adopted, on its organization in 1930, the policy of charging the medical members of the Committee with the final decision as to therapeutic usefulness and leaving the decision as to pharmaceutic necessity and tests for purity and strength to the pharmacist members. Carrying out this policy the entire group of medical members of the Revision Committee are members of the Sub-Committee on Scope. To these 18 physicians, practitioners, teachers, soldiers, has been given the onerous task of selecting the approximately 600 substances which enter the U. S. P. XI.

The Scope Sub-Committee must determine what yard-stick shall measure the eligibility of a medical substance for admission. Obviously, all agents used by the profession, even if possessing medicinal properties, cannot be admitted. Therefore, the Sub-Committee on Scope has determined that a substance must be a therapeutic necessity to obtain admittance. To be considered a therapeutic necessity it must appear that its usefulness is recognized by the prevailing medical opinion; that its pharmacological activity is not completely shared by a drug or drugs already admitted; that its use is, in the aggregate, large enough to make its standardization desirable; and, finally, that its composition must not be secret, nor may it be privately controlled. Not all agents possess action making them equally important therapeutically. Laboratory study, methods of assay, animal experimentation, etc., are all of value in determining drug action, but the final arbiter

* Read at the Chicago meeting of the American College of Physicians, April 20, 1934.

of therapeutic usefulness must be the clinician. Where clinical opinion is uniform or unanimous with respect to the value of a drug the work of the Scope Sub-Committee is easy, but it often happens that clinical opinion is so divided that decision as to admission is difficult. In such instances the competency of observers, the accuracy of recorded observations, as well as the number of such observations, must be digested by the Committee. It follows that many drugs favorably reported on by the pharmacologist fail to achieve a permanent place in the sun.

U. S. P. X carried 622 titles and nearly 400 of these were admitted to U. S. P. XI without a dissenting vote. A number of the remaining have been admitted by a two-thirds vote of the Sub-Committee on Scope. Nearly 200 new titles suggested by Committee members and others and every title in the 1931 New and Non-Official Remedies issued by the American Medical Association have been studied by the Scope Sub-Committee. The number of titles that will appear in the U. S. P. XI cannot yet be stated, as the work of the Scope Sub-Committee has not been completed, but approximately 600 will appear. The new British Pharmacopoeia (1932) has 586 titles.

As a final check for the Sub-Committee on Scope, substances occupying a neutral zone are referred to the Sub-Committee on Therapeutics, composed of nine physicians interested in therapy. If this number appears too small a group to determine matters of such great importance, the objectors are answered by the reminder that the medical profession had adequate opportunity to have a larger influence in the work of revision. Incorporated Medical Colleges and Schools of incorporated Colleges and Universities, incorporated State Medical Associations, the American Medical Association, the U. S. Army, Navy and Public Health Service, are each entitled to send three delegates to the Pharmacopoeial Convention. The delegates to the Pharmacopoeial Convention select the members of the Revision Committee. Nine State Medical Associations availed themselves of the opportunity to send delegates to the 1920 Convention and 26 medical schools felt a similar interest.

Deletions. That substances admitted during one revision may be omitted in some succeeding revision is but evidence of growth in medical science and the fallibility of judgment. No criticism attaches to the first factor, in fact, growth is welcomed; the second factor does not bulk large in the work of revision because of the detailed consideration given a new substance before admission and a fixed purpose to avoid radicalism. But drugs once considered a therapeutic necessity do come to be displaced by better ones, sometimes the result of added knowledge of etiologic factors, often the consequence of better understanding of pathologic processes and equally as frequently because of new developments in drug manufacture or discovery.

Acting under these broad principles substances official in U. S. P. X have been deleted from U. S. P. XI. About 100 titles found in U. S. P. X have not been admitted to U. S. P. XI. It has not appeared wise to carry impedimenta in the Pharmacopoeia and an effort is being made to eliminate

most of the titles representing unnecessary substances. The Scope Sub-Committee has endeavored to have the Pharmacopoeia represent leadership in therapy and not gravitate to the lowly estate of becoming the repository of the heirlooms garnered from the field of empiricism.

Both the medical and pharmaceutical professions are apprised of proposed deletions as the work of revision progresses and arguments in favor of retaining proposed deletions are welcomed. Either the members of the medical profession have generally approved the deletions proposed or it is peculiarly indifferent, since relatively few objections have been filed. Numerous and frequent objections have been heard from the pharmacists, individually and collectively. One would expect to find the attitude reversed, but the conclusion is inescapable that physicians are content to obtain much of their therapeutic information from the pamphlet left with the sample in their offices by a representative of a manufacturing pharmaceutical house. Too small a number of physicians feel it necessary to buy new texts on pharmacology and therapeutics and the number who purchase a copy of the United States Pharmacopoeia is almost negligible.

It has been the purpose of the Revision Committee to make the Pharmacopoeia sufficiently catholic to cover all reasonable therapeutic needs. With the substances it contains any physician should be able to carry on the exacting demands of his practice regardless of specialization. It is realized that one of the reasons the Pharmacopoeia is not more popular with physicians is because of their unwillingness to write prescriptions containing the basic agents desired, with individual directions for the pharmacist for compounding. Most physicians of this generation have either never acquired or have neglected the art of prescription writing. They prefer to write for some trade-named preparation compounded by the manufacturing house. They ignore the significant weakness of fixed ingredients, of the presence of substances the patient prescribed for may not need, of the added cost to the sick to cover proprietary rights and advertising campaigns. If the costs of medical care are too high, not a little of that cost is chargeable to physicians who prescribe high-priced drugs frequently having no greater value than older or less expensive ones.

Prescription Surveys. Another yard-stick with which to measure therapeutic usefulness consists in Prescription Surveys. The object of these has been to determine the actual use of both official and non-official medicines by physicians in their prescriptions. Surveys of this nature have been made at intervals since 1885 and the latest one was made in 1931 under the auspices of the United States Pharmacopoeia and the National Formulary jointly. The object of this survey was to obtain authentic information regarding the items in prescriptions and the number of times each ingredient appeared in prescriptions written by physicians and compounded by pharmacists. The survey covered many sections of the United States, hence it was fairly representative. It also was intended to discover the extent of the use of proprietaries.

One hundred and twelve thousand prescriptions were thus studied. It was estimated that 115 million prescriptions were written during the year (1931) studied. There are two ways of expressing extent of use: (a) the number of times a given drug appeared in an arbitrary group, say 5000; (b) the total number of times a substance was estimated as being used during the year. For example, a drug may be used but once in 5000 prescriptions; this appears an infrequent use, but when it is shown that such frequency means it was used 50,000 times during the year the significance is materially altered.

Some interesting features have been uncovered by this survey. United States Pharmacopoeia titles appeared in about 70 per cent of the prescriptions studied, while non-official titles appeared in 30 per cent. About 200 of the U. S. P. X titles rarely or never appeared in the prescriptions studied. The numerical rank of appearance of drugs occurring in these 112 thousand prescriptions proved illuminating. Codeine was used three times as often as morphine; sodium bicarbonate was used more than three times as often as quinine sulphate; essence of caroid was used twice as often as dilute hydrochloric acid; sodium bromide was used five times as often as sodium iodide; the tincture of gentian compound was used more frequently than tincture of digitalis; syrup of tolu was used 13 times as often as syrup of senega; unguentum hydragyri ammoniati was used six times as often as unguentum sulphuris.

Such surveys are of much statistical interest, but too much significance should not be given to mere frequency of use. Codeine sulphate was prescribed 74 times as frequently as codeine phosphate. The explanation probably lies in the familiarity with sulphate salts of alkaloids. Morphine, atropine, and strychnine being old and much used drugs, have familiarized the physician with sulphates, and when he thinks of codeine he probably only thinks in terms of a sulphate. Certainly the frequency of use of the sulphate is no sort of evidence of the superiority of the sulphate over the phosphate. Tincture of gentian compound was used oftener than tincture of digitalis, but the relative value of each is not so determined. Sodium bicarbonate was used oftener than any other drug in the Pharmacopoeia, and yet one could practice medicine without it and not raise his mortality rate. Merely because doctors used Schleich's solution, and it contained opium, did not mean that opium has any local action. The greater use of infusion of digitalis does not prove it to be a superior preparation to pulvis digitalis folium.

The Pharmacopoeia should contain a list of drugs of similar action to permit of variations for obvious reasons. But the book should be a leader of therapeutic thought, not a book of antiquity.

Patents and Trade-Marks

The Committee on Revision was instructed by the Pharmacopoeial Convention to "admit into the Pharmacopoeia a carefully selected list of

medicinal substances of known origin, but no substances or combination of substances shall be introduced if the composition or mode of manufacture be kept secret."

The Conference of Pharmaceutical Law Enforcement Officials recommended to the Pharmacopoeial Convention that proprietary medicines be not admitted into U. S. P. XI.

A privately controlled drug is a proprietary drug. Whether it is used singly or whether more than one is used, should create no confusion in the definition. Neither does it matter if the drug is well known, possesses therapeutic value and is in general use; if privately controlled it is a proprietary. Such a drug has a name and standards of strength or purity as determined by its owner, and he may alter such standards when and as he chooses. If such a drug or product is admitted under some other name or if some other standard is set up for its preparation, it ceases to be the same drug or product; in addition, if a patent or trade-mark has been issued, the Pharmacopoeia would become liable for ignoring property rights. On the other hand, if the Pharmacopoeia should admit a proprietary product with the name and standards of the owner, it has only advertised a privately controlled preparation.

However, if a drug is marketed under a controlled name, yet other houses may produce and sell it under some other name, the Revision Committee may admit it under a distinctive title if it is thought to be a therapeutic necessity. Aspirin is an example of such a product. Any manufacturing drug house may make acetylsalicylic acid and sell it under a name not already coined. The United States Pharmacopoeia may admit such a product, select a name for it and set up standards of strength and purity. Or if a privately controlled drug loses its proprietary character it may be admitted under some distinctive name. Not a few drugs now in the Pharmacopoeia had such an origin. Fowler's solution, paregoric, Lugol's solution, Basham's mixture, are well known examples of proprietary, even "patent medicines."

After much discussion the Revision Committee adopted the following general rules with regard to drugs covered by patent or trade-mark rights:

(a) A drug covered by patent or trade-mark rights should not be considered for admission unless it possesses pharmacological activities establishing it as a therapeutic necessity.

(b) No trade-marked or patented names shall be admitted. It shall be given either a chemical name or a short coined name not patented or trade-marked.

(c) The date of expiration of patent or trade-mark shall constitute a definite factor in the decision to admit or not. If the patent expires early in the decade during which the Pharmacopoeia is official, such patent or trade-mark might not prove a serious objection to admission.

(d) The approval of the patentee or trade-mark owner should be accorded to the proposal to admit a drug so controlled.

Another interesting phase of this proprietary medicine problem was the proposal to carry under the official title of a drug all of its proprietary names

as Synonyms. To illustrate: Insulin is admitted to the Pharmacopoeia under the title *insulin;* it was then proposed that such a proprietary name as Iletin be carried as a synonym. The manufacturers of Iletin would thus be given a costless, yet almost priceless, advertisement. It is the judgment of the Revision Committee that an iodized oil should be admitted to the Pharmacopoeia. Products of this nature are marketed by a number of firms, each having a distinctive trade name of its own. A few examples which may be cited are Lipiodol, Lipoiodine, Iodipin. Should an iodized oil be admitted it would not be wise to carry under its U. S. P. XI title the names just mentioned as synonyms. And, unless each of these products was made exactly the same way and unless each was of the same strength as the one admitted, the other trade-marked products would not be synonyms.

The following extract from the correspondence with the Rockefeller Institute relative to the admission of Tryparsamide affords an insight into some of the perplexities of trade-marks and patents and synonyms:

> . . . The patent and trade-mark rights relating to Tryparsamide are held by the Rockefeller Institute and the patents in the United States expire in 1935. . . . Merck and Company has been licensed by the Institute to manufacture Tryparsamide in the United States and in certain other countries. For . . . reasons the Institute now plans to continue to allow Merck and Company the right to sell Tryparsamide under its trade-mark rights after its patent rights have expired. . . . The Institute would have no objections whatsoever to the inclusion of Tryparsamide in the Pharmacopoeia or . . . its proper chemical name. However, we would not be prepared to abandon the name Tryparsamide or to encourage the substitution of any other title . . . which might tend to create confusion.

The Revision Committee can admit this product under its chemical name or some other coined title and set up standards for its manufacture, but if the word "Tryparsamide" is not introduced as a synonym a large part of the profession would not recognize it as Tryparsamide and they would continue to prescribe the original patented article.

Favoring the plan of using synonyms, it was urged that the proprietary name was often the one best known to the physician and that he could thus better identify the official drug. It was further urged that such a plan would make more effective teaching the use of official drugs to medical students. The Revision Committee has decided against the proposal to admit such names as synonyms by a large majority.

The whole question of patents and trade-marks in medicine is becoming one of increasing importance to the profession beyond the scope of Pharmacopoeial revision. One wonders if the members of the profession are actuated by impulses involving pecuniary benefit directly or indirectly to a greater degree than obtained in the generation of physicians this one succeeded. The magnanimity and fine scientific spirit which gave serums and vaccines to the world contrasts strongly with the advent of insulin, ventriculin, viosterol or scarlatinal toxin.

The arguments made, or rather I should say the explanations offered

in justification for seeking and obtaining patent and trade-mark rights are replete with protestations of scientific interest, of jealous concern for the welfare of the sick and solicitude for the public's purse. One of these writes, "The main object in securing patents and trade-mark rights and in licensing one company to manufacture and sell the drug has been to insure to the public a product of acceptable quality at a reasonable price."

Another representing a group controlling a product writes:

> The function of the Committee is to protect the public as far as possible against inadequate preparations. . . . Thus it falls within our duties to try out new preparations, . . . if they are successful, to approve them for distribution. If they are unsuccessful, in our opinion, it is our duty to stop their distribution. . . . We regard the public welfare as of far greater importance than any personal relationships. . . . We shall not hesitate to institute whatever legal proceedings are indicated.

One wonders if a patent issued on a given biological product enables a committee owning the patent to censor and control all investigation of a transmissible disease problem; one wonders if a patent is intended to interfere with independent study and experiment; one wonders who protected this same public while experimental work was being done on the product for which a patent has been issued.

Studying the broad field of research medicine, it is significant that the favorite plan now is to give some university or laboratory or committee the patent and trade-mark rights and to assure the public, as well as the profession, that all profit is to be devoted to further research. Such a plan assures the individual physician immunity from the charge that he is pecuniarily interested in the product. But it does not suppress the thought that he has made himself valuable to his institution and salary increases are not impossible.

Are we drifting away from the fine spirit of our fathers? Is the beneficent altruism of the old Masters in danger of being lost?

As a means of checking the present tendency it is suggested that the patent and trade-mark laws as pertaining to medicine be modified to the extent that when and if a product be admitted to the United States Pharmacopoeia the patent and trade-mark rights end with such admission. Were this done, coupled with interim revisions, the public, concerning which such solicitous anxiety is manifested, would be adequately protected.

Federal and State Food and Drug Acts

Revision of the Federal Food and Drug Act in some form will, in all probability, be enacted into law during the present Congress. The details, merits or demerits of this proposed legislation are not proper subject matter for this discussion, but the relation of the Pharmacopoeia to such legislation, both National and State, has a real significance.

The United States Pharmacopoeia is not a governmental instrument. The Pharmacopoeias of most other countries are issued by the government,

hence are governmental institutions. The United States Pharmacopoeia is made possible through the coöperative labor of the medical and pharmaceutical professions. It did not receive any sort of recognition by the Federal government until the passage of the Food and Drug Act in 1906. At that time the necessity for having standards of purity and strength was recognized and the United States Pharmacopoeia was selected as the instrument for setting up such standards. This recognition is a most unusual one in that it is the only professional contribution which has been given such distinction. Stripped of all superfluous verbiage, it means that two professions uniting in a common effort to establish high standards in what amounts to self-regulation have done so to the extent that the Federal government has adopted those standards for purposes of enforcement of Federal laws. If an added responsibility were needed to encourage each subsequent Revision Committee to carry on, this governmental relation surely affords it. Since the major portion of the work of determining standards of purity and strength has been done by the pharmaceutical members of the Revision Committees, past and present, theirs is the larger share of credit for the present status.

The National Formulary has been included in previous Food and Drug Acts as one of the standards for determining violations of the Federal Law as to purity, etc. The present and pending bill in Congress introduces another text into the enforcement picture by defining the term "official compendium" as meaning the United States Pharmacopoeia, the Homeopathic Pharmacopoeia of the United States and the National Formulary.

Since the Homeopathic Pharmacopoeia has not been revised since 1914, it would appear that the proponents of the pending legislation have peculiarly overlooked the progress of medicine, pharmacy and chemistry, for two decades. It is admittedly difficult to set up an "Official Compendium" to be used in enforcement of a Federal Food and Drug Act without, at the same time, making such texts, in effect, the law. Congress has the power, it is thought, to recognize a work as a statutory authority in existence at the time a bill is passed; it may even include supplements to such a volume. But the pending bill would make all future editions and supplements likewise the law, and by such declaration would give future Revision Committees the authority to change standards when and if deemed desirable. Since the Revision Committees of these texts are not officers of the Government, the question might well be raised, is this an "unconstitutional delegation of legislative authority?"

The pending legislation provides, in addition, that the Secretary of Agriculture may prescribe texts or methods of assay for determining whether or not a drug complies with legal standards "when such texts or methods of assay as are prescribed are insufficient" after he has brought the fact of such insufficiency to the attention of the Revision Committees of such compendium and they have failed to provide adequate standards.

The officers of the Food and Drug Administration of the Department

of Agriculture are the enforcement officers of the Federal Food and Drug Law. This group is represented by delegates to the Pharmacopoeial Convention and has participated in work of revision since. The Bureau of Standards, likewise, is represented. By such coöperation the Pharmacopoeia is made to anticipate governmental needs through interim revisions when necessary.

The tendency of the courts to admit a wider variety of proofs of illegal manufacture or shipment of drugs outside the Pharmacopoeial standards must be noted. In the recent decision of the U. S. District Court of the Eastern District of New York, in what has come to be known as the "Ginger" case, it was held that: "There is no reason to hold that the non-correspondence of the extracts shipped with the standard of the Pharmacopoeia must be shown only by chemical analysis. On the contrary, it may be established in any other logical and convincing way."

This attitude is further evidenced by the statement of an official of the Food and Drug Department that in the event the Pharmacopoeia omitted certain agents, the Government would not be likely to permit such omission seriously to handicap the department in its work of preventing impositions on the consuming public.

Another interesting angle in the relation of the Pharmacopoeia to the Federal Food and Drug Act now in force has developed in consequence of the interpretation of the Solicitor of the Food and Drug Administration of what part of the text was applicable. The Act requires compliance with the "tests for quality, purity and strength" as laid down in the Pharmacopoeia, but the Solicitor has ruled that this be interpreted as excluding such parts of the text as definitions, formulae and descriptions.

In the case of some titles in the text the definition and the description are important as to identification and even standardization. It has been quite generally accepted that the whole text of a drug was intended to be used for the establishment of uniformity, as well as efficiency.

To meet this situation it is proposed to introduce in the forthcoming Pharmacopoeia a "General Notice" definitely stating that all sections of a monograph, unless specifically exempt, are to be recognized as a part of the standard.

"Interim Revision"

It is recognized by physicians, pharmacists and government officials alike that a decennial revision of the Pharmacopoeia does not keep it abreast of scientific medical development. Many new data accumulate, now, in a 10 year period; new therapeutic agents come into use at a rapid rate and refinements of manufacture, assay, etc., render old methods and standards rapidly obsolete. To appreciate the extent of this development one needs but to call to mind a few illustrations: liver extract, insulin, vitamins.

The cost of more frequent complete revisions, encompassing the issuance of an entirely new book, is prohibitive. If sectional revisions be

done the difficulty of giving them a permanent form, as well as necessary publicity, becomes a matter of practical importance. Even when the new matter involves the admission of a new agent and even if added as a "supplement," the matter of indexing offers a problem. If the change applies to but a part of the text on a given agent, the difficulty becomes appreciably more intricate.

A loose-leaf type of book, allocating one or as many sheets as necessary to each separate subject, permitting removal of the old text and insertion of the new, would seem to be the simplest method for keeping the text up to date. A nominal charge could be made for newly-revised sheets; a revised index could be made yearly and supplied each subscriber. The plan at present agreed upon to keep the U. S. P. XI revised consists in: (a) issuing a printed supplement on the first of each year; (b) the statement that each change so made becomes official on January 1, coincident with issuance; (c) that as changes are decided upon announcement be made in the medical and pharmaceutical press of the country; (d) that the supplements be of uniform size with the original text; (e) that a revised index be issued with each annual issue of supplements; (f) that a binder be supplied for the preservation of supplements as issued; (g) that a page of coupons be included in the original copy of the U. S. P. XI, the owner of the book to fill out a coupon for each annual supplement revision, which enables him to obtain from the publisher a copy at a nominal cost; (h) the issuance at the end of five years of the original volume with all interim revisions included. This latter proposal has not been definitely determined.

The success of such a general plan of interim revision would depend upon many factors wholly beyond the control of the Revision Committee and the Board of Trustees. If the owners of the volumes did not co-operate to the extent of both obtaining and preserving the copies of interim revisions, much confusion and error would obtain. In court procedure, for example, the necessity for establishing the text of the copy of the U. S. P. XI revised to January 1 of the current year would be obvious. Another problem is presented in the books on pharmacology used by physicians and students. The text of these books is based on the United States Pharmacopoeia and the authors would meet a practical difficulty in dealing with interim revisions.

The advantages, however, are so obvious that making the plan of interim revision workable becomes a necessary duty and its accomplishment will be the outstanding achievement of Pharmacopoeial revision. Reference has been made to some of the necessities for and advantages of an up-to-date Pharmacopoeia under the section of this paper on the scope of the Pharmacopoeia.

Original Study

In revising the Pharmacopoeia the medical and pharmaceutical literature is studied so that the last information available on all subjects may be

utilized. This applies to such subjects as are admitted because of therapeutic usefulness, as well as pharmaceutic necessity. Supplementing such study as the Committee on Revision has time or qualification for doing, the By-Laws of the United States Pharmacopoeia Convention authorize the employment of experts in the various fields studied. These studies began as early as 1926, preparatory to the revision of the present Pharmacopoeia.

The advantages of this plan are apparent, but three merit emphasis in the present discussion. (1) Such workers are already familiar with the current literature on the given subject, as well as the technical aspects involved. (2) By enlisting the interest of scientists, practical workers and students, as well as universities, colleges and laboratories, a greater and more general interest in the Pharmacopoeia is obtained. (3) Such coordination and intensive study means a saving in both time and money. Approximately $10,000 have been expended on this phase of the work of revision for the coming issue.

In addition to these groups of experts the services of another valued group have been made available through the coöperation of auxiliary members. These auxiliary members were individual physicians, pharmacists and scientists who were invited by the Revision Committee to coöperate in the work of revision because of special qualifications or interests. More than 200 auxiliary members have been elected to these positions and their contributions have been noteworthy.

Yet a third group has done yeoman service in the work of revision. The United States Pharmacopoeia is the legal standard for the Philippines, Puerto Rico and Hawaii and the adopted standard of the Republic of Cuba. Representatives from these islands have, on invitation, participated in the work of revision.

Finally, the work of revision has been materially advanced by the coöperation of the Pharmacopoeial Committees of Great Britain and of Continental Europe. Switzerland, Holland and Germany have issued new Pharmacopoeias since 1926 and much of their new material has been translated by the Committee of U. S. P. XI for study by the various sub-committees.

Vitamins

An optional method for the biological assay of one of the potent principles of cod liver oil was included in the U. S. P. X. By this act the United States Pharmacopoeia took advanced ground ahead of the Pharmacopoeia of other countries.

This method of assay was (a) optional, (b) provided that oil should contain " at least 50 units per gram," (c) provided for vitamin A assay only.

It, therefore, did not establish a standard of A potency, but rather determined the lowest value an oil might have to permit labeling as a United States Pharmacopoeia product. Neither did it recognize the D

content of cod liver oil. The method of biological assay established as the end point the relief of symptoms of vitamin A starvation in young albino rats with a specified gain in weight during the test period. The cure of xerophthalmia has been urged as a superior biologic criterion; while such a criterion is more convincing qualitatively, it is more indefinite quantitatively than the criterion of growth recovery for a 35-day period.

A presumptive defect in the method of the U. S. P. X lay in the influence which other possible factors might have over the weight decline of the test animal while vitamin A was withheld, as well as such influence on the weight recovery period during the cod liver oil feeding period. One need merely mention the physical character of the ration, the amount of protein consumed and the presence of vitamins B and D.

An assay method for vitamin D had also become a necessity by virtue of increasing knowledge of its importance. The method of basing the unit for A on the daily dose, while the unit for D was based on the total dose, gave results indicative of a marked apparent discrepancy in A and D content in a given sample of oil. Some method whereby this apparent discrepancy might be reconciled was urgently needed.

Another important question in the biological assay of cod liver oil concerns the quantitative interpretation of the data of A and D assays. In all bio-assay work a certain deviation of biological response is usual. In other words, should this deviation response be ignored or made use of by specifying the unit dose in terms of percentage of positive responses? Further, some appreciation of the importance of the variations of statements on the labels of different brands of cod liver oil was made necessary because of differences in standards for potency adopted by the various distributing firms. Likewise, some uniformity in labeling was recognized as a necessity. Some firms labeled their product in terms of units per gram, others in terms of units per ounce. This lack of uniformity was confusing alike to the doctor, the druggist and the patient.

The Permanent Commission on Biological Standards of the Health Organization of the League of Nations has issued a standard for vitamins. The United States has a representative on this Commission.

Through its Board of Trustees the U. S. P. XI is coöperating with the medical and pharmaceutical professions of other countries to reach an agreement on an international standard for vitamins.

The Pharmacopoeia has set up a Vitamin Advisory Board; this includes a group of laboratories now engaged in the work of developing satisfactory vitamin assay methods for vitamins A and D. A composite sample of cod liver oil labeled " reference cod liver oil " has been distributed among the workers to be used as a standard of comparison in assaying the vitamin content of both foods and medicines. The members of the American Drug Manufacturers Association, the Federal Food and Drug Administration and a number of laboratories in various universities are coöperating with the U. S. P. XI in this work. Without this contribution on the part of

vitamin experts the expense of this work would be large enough to make it impossible for the Pharmacopoeia to carry it on.

The most important question touching the work on the biological assay of cod liver oil for A is the criteria of A deficiency in experimental animals. None adopted thus far are 100 per cent perfect and are, at best, a matter of comparison.

The following standard has been recommended for adoption:

The new U. S. P. XI vitamin A units are to be identical with the international units. The minimum vitamin A standard for U. S. P. XI cod liver oil shall be not less than 600 international units.

The study of vitamin D has led to the recommendation that its potency in cod liver oil should also be expressed in terms of units. A unit is to be defined as the minimum average daily amount of cod liver oil required to produce a continuous narrow line across the metaphysis of a leg bone in four out of six rats in each group prepared under conditions specified for the assay.

It is well known that cod liver oil shows much less variation in its vitamin D potency than it does in vitamin A content. Notwithstanding this relative uniformity the British Medical Research Council has recommended the adoption of a standard ergosterol solution to serve as a measure for vitamin D potency of substances containing or claiming to contain this vitamin. This ergosterol was prepared from yeast by drying and dissolving in alcohol and subjecting the end product to irradiation from a mercury arc lamp. It was found that such a preparation was soluble in olive oil and retained its potency unchanged for as long as two years if kept below 0° C. The British Medical Research Council has recommended that the potency of this antirachitic substance be measured in terms of units and that either the roentgen-ray, "Line Test" method or chemical analysis of bones of experimental animals be used in estimation of vitamin D.

The Council defines the unit of vitamin D "as the antirachitic potency of a quantity of irradiated ergosterol corresponding to 0.0001 mg. of the ergosterol used in its production." One c.c. of their standard solution, therefore, represents 1000 units of vitamin D activity.

The chief commercial supply of vitamin D in this country comes from irradiated ergosterol. Through the Council on Chemistry and Pharmacy of the American Medical Association this substance has come to be known as Viosterol. It is dispensed in a vegetable oil and is about one hundred thousand times as potent as an antirachitic as cod liver oil.

The Special Committee of the U. S. P. XI has recommended that the minimum vitamin D standard for the U. S. P. XI cod liver oil shall be not less than 85 international units.

Latterly much discussion has accumulated in the files of the Revision Committee concerning the definition of cod liver oil. A three-cornered discussion has just been concluded, the participants being the officials of the Bureau of Fisheries, the Food and Drug Administration and the Sub-

Committee 8, of the Revision Committee U. S. P. XI. The point at issue was whether cod liver oil should be defined in the interim revision text as "the fixed oil . . . obtained from fresh livers of *Gadus morrhua linne* and of other species of Gadus" or "other species of the family Gadidae."

To the average physician it might seem a mere peccadillo whether the oil he prescribes for Junior sprang from the royal "species of Gadus" or emanated from the plebeian "family Gadidae." No doubt even Junior would be disdainful as to the source of his daily vitamin A, paraphrasing Shakespeare in asserting that "Cod liver oil from any other source would smell as malodorously." In this discussion commercial interests, as usual, took a hand. The total domestic consumption of cod liver oil is nearly five million gallons, an average of two-thirds of a pint for each man, woman and child in the United States and her colonial possessions! Ninety-four per cent of this oleaginous river flows into the States from foreign countries; two countries, Norway and Newfoundland, supply 72 per cent of our imported oil. These countries restrict the source of the oil to the genus Gadus. To them the family Gadidae is anathema.

To the Revision Committee the vitamin content and the esthetic qualities of the oil must be assured—the rest is twiddledee or tweedledum.

Color Standardization

Color, at first thought, appears simple and elemental. White light passed through a prism and projected on a screen produces a band of light called a spectrum. This spectrum presents a range of colors with violet at one end and red at the other, while indigo, blue, green, yellow and orange lie between, in the order named. The shades between these primary colors which the eye can recognize and name are a bit limited; they are estimated at from three to 130.

The U. S. P. X used 287 different color names. The importance of a color standard is recognized by the fact that these color names are used more than 2400 times in the book. During the 10 year period following the last revision some research study was authorized by the Board of Trustees. The result of that study was a very instructive color exhibit by the Committee at the Pharmacopoeial Convention May 13, 1930. During the session of the Convention the first Color Conference was held and more than 100 experts participated in the work of establishing workable standards for color estimation and uniformity in nomenclature. Out of this Conference developed an "Inter-Society Color Council," to which representatives were accredited to chemical, architectural, physical, optical, engineering, pulp and paper, painters and decorators and motion picture societies. More than a score of private individuals interested in color description and specification also participated.

While the United States Pharmacopoeia initiated this study, it is evident that no marked changes in nomenclature could be made without the co-

operation of the many diverse interests of art, science and industry. In short, in the language of the Chairman, the definitions on limitations of color names should be " so accurate that science will accept them; so broad that science, art and industry can use them; so popular that the public can understand them."

The Pharmacopoeia is interested in two primary color problems, (a) the scientific standardization of color names, (b) the background color of " poison " labels. Experts are now at work checking the color names used in the coming text of the U. S. P. XI, correlating it with the color nomenclature being studied by the Council as a whole. This accomplishment will make the U. S. P. XI the first scientific publication to carry a color nomenclature based on a scientific foundation.

Percentage Solutions

When a physician writes a prescription for a preparation in solution in a given per cent he thinks he has given the pharmacist as specific directions as are necessary. As a matter of fact, the pharmacist recognizes that the term *per cent* has different meanings when used under varying conditions. He wonders if the physician means the sum of the percentages of the ingredients or the composition in terms of the finished product. The physician probably thinks, as a matter of mathematics, that the sum of percentages of ingredients means 100. The pharmacist remembers that a 10 per cent solution of sodium chloride may contain 95 per cent of water. Again, the physician writes for a " saturated solution " of potassium iodide and later the same order is written for sodium iodide. When the patient takes 30 drops of the first he is taking a solution containing 103 per cent of potassium iodide, while in the latter prescription there is 120 per cent of sodium iodide.

To obviate some of the uncertainties in prescription work it is proposed to carry under the caption, " General Notices " of the forthcoming Pharmacopoeia a statement somewhat as follows:

> Per cent weight in weight to be expressed by the symbol W/W and means the number of grams of an active ingredient in 100 grams of the solution.
>
> Per cent weight in volume to be expressed by the symbol W/V and means the number of grams of an active ingredient in 100 cubic centimeters of the solution.
>
> Per cent volume in volume to be expressed by the symbol V/V and means the number of cubic centimeters of an active ingredient in 100 cubic centimeters of the solution.
>
> That the expression per cent when used without qualification is to be interpreted as meaning: for solution of solids in liquids, per cent, weight in volume; for solution of liquids in liquids, per cent, volume in volume; and for solutions of gases in liquids, per cent, weight in volume.

These terms are equally applicable to the metric and apothecaries' systems; e.g., a 1 per cent solution prepared under the metric system would contain one gram of a solid or one cubic centimeter of a liquid in enough of the

solvent to bulk 100 cubic centimeters of the finished product. When prepared under the apothecaries' system 4.6 grains of a solid or 4.8 minims of a liquid in enough of the solvent to bulk one fluid ounce of the solution.

Of course, in pure science percentage composition tables are expressed in terms of per cent by weight. It is not common practice, however, in the United States to weigh liquids. Some sanction to the proposed recognition in the U. S. P. XI may be found in the recommendation for adoption by all State Boards of Pharmacy of such a method by the National Association of Boards of Pharmacy; the adoption of such a method by the Conference of Pharmacy Teachers of the American Association of Pharmacy Colleges; the definition of percentage solutions and acceptance of the metric W/V solution in the book, "Useful Drugs," published by the American Medical Association for the guidance of faculties of medical schools and State Medical Examining Boards. It may be further noted that the British Pharmacopoeia of 1932 introduced a similar statement under the heading, "General Notices," in an effort to establish uniformity in practice. The introduction of such a statement as proposed into the U. S. P. XI will give official sanction to the metric W/V basis for making percentage solutions and make prescribing more definitely uniform.

EDITORIAL

CHEMICAL FACTORS IN THE BEHAVIOR OF THE VEGETATIVE NERVOUS SYSTEM

WITHIN the past decade a new concept of the method of transmission of the effects of nerve impulses has developed. Dale recently has summarized the contributions and development of knowledge in this field. The first suggestion that a chemical agent acted as an intermediary between nerve stimulation and effector response was made by Elliot in 1904. After noting the similarity between the action of epinephrine and the stimulation of sympathetic nerves, he postulated that sympathetic nerve fibers liberated epinephrine at their endings; the epinephrine, he implied, might be the chemical intermediary between nerve impulse and effector response. Dixon was the first to suggest that the parasympathetic nerves might also release a chemical substance at their termination. The lucid experiments of Otto Loewi, in 1921, demonstrated for the first time the tenability of the foregoing hypothesis. He showed that the vagus nerve of the frog produced its effects on the heart by liberating an inhibitor substance which he termed "Vagus Stoffe." The fluid obtained from such a heart could be transferred to another heart, and again would exhibit an inhibitory or vagus effect. Loewi found this inhibitor or vagus substance corresponded to acetylcholine by all known tests.

The investigation of the part played in physiology by this derivative of choline forms an interesting chapter in medical research. Acetylcholine was synthesized by Baeyer in 1867, and its intense physiologic properties were discovered by Hunt and Taveau in 1906. It was not until 1914, however, that it was known to occur in nature, when Dale found it present in a sample of ergot. At this time Dale noted the remarkable similarity between the action of this substance and the effect of stimulation of the parasympathetic nerves. Acetylcholine causes inhibition of the heart, increase in intestinal tonus, and dilation of small arterioles. These actions can be abolished by atropine. It also has a third type of effect similar to nicotine, that is, there is a rise in blood pressure which is presumably due to stimulation of sympathetic ganglia, together with liberation of epinephrine.

Acetylcholine was first isolated from the animal body in 1929 by Dudley and Dale, who found it in extracts of the spleen of the ox. Recently, Chang and Gaddum have found it present in large amounts in the placenta of women. In an analysis of various body tissues they found the largest amount of "acetylcholine equivalent" in those tissues, the activity of which is controlled by the parasympathetic nerves.

It is almost certain at present that acetylcholine is the chemical transmitter of parasympathetic effects. Englehardt obtained a substance after reflex production of the autonomic actions of the third cranial nerve, which was similar to Loewi's "vagus substance" and presumably was acetylcholine.

Similar results have been obtained from stimulation of the chorda tympani nerve. Dale and Feldberg collected the substance released in the wall of the dog's stomach after stimulation of the vagus nerves and found it to correspond entirely to acetylcholine.

The fact that stimulation of the sympathetic nerves released a chemical substance was also first demonstrated by Loewi. The vagus nerve in the frog contains some sympathetic fibers, and at times stimulation caused acceleration of the heart. In these instances he found that the fluid from the heart transmitted an accelerator or epinephrine-like effect to another heart. Cannon and his coworkers recently have shown that, in a suprarenalectomized animal, stimulation of the lower end of the sympathetic chain caused release into the blood of a substance producing sympathetic stimulation in other organs. This substance closely resembles epinephrine. Cannon has called this substance sympathin and has expressed the belief that it is not identical with epinephrine. He stated that there are two types of sympathin: (1) Sympathin E, given off by smooth muscle which is stimulated to contract by sympathetic impulses and (2) Sympathin I, given off by smooth muscle which is inhibited by such impulses. Bacq has demonstrated that stimulation of the cervical sympathetic nerves causes release of a substance in the aqueous humor which is either epinephrine or closely related to it.

All evidence to date, then, points to acetylcholine as the chemical transmitter of parasympathetic effects and epinephrine or a closely related substance of sympathetic action. There are outstanding exceptions to this rule, so that Dale suggested the terms " cholinergic " and " adrenergic " to indicate the function of nerve fibers. The sweat glands of the cat and of the hand of man, although supplied by fibers of sympathetic ganglion cells, respond but little to epinephrine, but are stimulated to secretion by pilocarpine or acetylcholine. Feldberg and Dale showed that stimulation of the sympathetic nerve supply to the foot of the cat caused liberation of acetylcholine. These fibers are therefore cholinergic.

The mode of transmission of nerve impulses across synapses has never been well understood, nor has it been explained how the nerve impulse passes from motor end plates to voluntary muscle. Recent evidence indicates that acetylcholine may intervene in both these situations. Kibjakow perfused the superior cervical ganglion of a cat, and found that something appeared in the fluid after stimulation of preganglionic nerves which on reinjection acted as a stimulus to activity. In other words, impulses are transmitted across a synapse by release of this substance. Feldberg and Gaddum, using the same technic, showed that the substance was apparently acetylcholine. It is interesting to note that stimulation of the splanchnic nerve to the suprarenal gland caused acetylcholine to appear in the blood of the suprarenal vein (Feldberg and Minz).

Acetylcholine is known to stimulate certain voluntary skeletal muscles in lower vertebrates and in mammals after the motor nerves have degen-

erated. Recently, Feldberg and Dale have shown that stimulation of the hypoglossal nerve (after causing the sympathetic fibers normally present in it to degenerate) results in the formation of acetylcholine.

It seems probable from the mass of evidence accumulating that chemical substances are released at all cytoneural junctures in the periphery to act as transmitters of nerve impulses. Perhaps the same is true of synapses in the central nervous system. Dikshit recently showed that a small amount of acetylcholine injected into the intraventricular fluid caused effects on respiratory activity similar to central stimulation of the vagus nerve.

The discovery of the substances concerned in chemical transmission of nerve impulses opens up a new field for clinical research and therapeutics. Acetylcholine itself is not useful clinically, as its action is too evanescent, and it must be given intravenously. Recently new derivatives of choline have been synthesized. One of them, acetyl-β-methylcholine, can be given orally and subcutaneously; its effects are less transitory, and it may be useful in certain diseases or disturbances of cholinergic nerves. This concept of the behavior of nervous activity will help to clarify many puzzling phenomena observed in disorders affecting the vegetative nervous system.

G. A. G.

BIBLIOGRAPHY

DALE, SIR HENRY: Chemical transmission of the effects of nerve impulses, Brit. Med. Jr., 1934, i, 835–841.

LOEWI, O.: Über humorale Übertragbarkeit der Herznervenwirkung, Pflüger's Arch., 1921, cxciii, 201–213.

CANNON, W. B.: The story of the development of our ideas of chemical mediation of nerve impulses, Am. Jr. Med. Sci., 1934, clxxxviii, 145–159.

REVIEWS

Acute Intestinal Obstruction. By MONROE A. MCIVER, M.D., Surgeon-in-Chief, Mary Imogene Bassett Hospital, Cooperstown, N. Y. 430 pages; 19 × 26.5 cm. Paul B. Hoeber, Inc., New York City. 1934. Price, $7.50.

This monograph contains a very complete presentation of both the experimental work upon the consequences of acute obstruction; and the clinical aspects of this condition. The toxic, bacterial and splanchnic paresis theories are discussed and full references given to the literature. The clinical and pathological varieties of obstruction are described in detail. There is a very complete and valuable presentation of the problems associated with diagnosis and treatment. The investigator who is interested in this field and the practicing clinician will find this a helpful study of an important subject.

C. H.

The Medical and Orthopaedic Management of Chronic Arthritis. By RALPH PEMBERTON and ROBERT B. OSGOOD. vii + 403 pages; 15 × 22 cm. The Macmillan Company, New York. 1934. Price, $5.00.

In this book Pemberton and Osgood have quite thoroughly covered the single type of arthritis known as Chronic Arthritis. Of the 14 chapters, six are devoted to the various phases of treatment; this is as it should be since "what to do" is more important to the patient than "what is it?" Encouragement is given to the patient rather than the opposite which is so often the case.

Chapter II presents the evolution of the terms of classification since 1857 and ends by offering the two most commonly accepted division titles, atrophic and hypertrophic. These names are both descriptive and simple and they avoid the weakness of the so often attempted, but rarely completed, efforts to classify strictly according to etiology, or pathology, etc.

The pathological and physiological phases of the subject are fully covered. Unfortunately the physiology is not as clearly understood as is the pathology due to the differences in availability of material, etc., but a complete analysis of the many theories is presented with a brief explanation relative to the authors' views on each phase.

The six chapters on treatment are quite extensive and cover practically all available methods for the alleviation of the disease. The value of each method is weighed on the scales of the authors' experience which is extensive. Emphasis is placed upon the fact that no cure-all is now known for chronic arthritis and that the results of treatment are dependent upon slow, painstaking, and consistent work with one or more methods. Strength is placed upon the upbuilding of the body in general and the care of all system functions, especially posture and bodily activities, and the gastrointestinal tract.

This book offers a complete review of the subject of chronic arthritis from as nearly an unbiased and neutral standpoint as is possible. At times the discussion seems a trifle diffuse. Due emphasis is placed upon the necessity of a minutely careful survey of the individual as a whole, weighing the relative values of the abnormalities discovered. It is pointed out that in most cases improvement will be attained if a careful and thorough routine is followed. The vital importance of *early* diagnosis and of early treatment is stressed. In the convincing presentation of the foregoing fundamental principles lies perhaps the chief value of this interesting monograph.

A. V.

An Introduction to Sex Education. By WINIFRED V. RICHMOND, Ph.D., Psychologist, St. Elizabeth's Hospital, Washington, D. C. 299 pages; 14 × 21 cm. Farrar and Rinehart, Inc., New York City. 1934. Price, $2.50.

This is the third book that Dr. Richmond has written on the subject of sex education, yet there is very little that is repetition in this series. This latest book is an attempt to clarify the thinking on the whole subject and to give a concise and scientific discussion of the problem. Although Dr. Richmond is a psychologist, she has had a broad experience with abnormal as well as normal psychology, and has been closely in association with the medical group at the federal hospital, and it is evident from her references that she has widely read the medical literature on the subject under consideration.

In these chapters she discusses general biology, biology of reproduction in man, sex in primitive society, marriage and the family, psychology of sex, specific problems preventing proper adjustment in sex, and problems complicating marriage. In her final chapter she very sanely presents a program of education. The physician will find this is a book that he can safely recommend to his patients without the fear of creating morbidity.

J. L. McC.

Clio Medica. German Medicine. By W. HABERLING, M.D.; translated by JULES FREUND, M.D. 160 pages; 11 × 17 cm. Paul B. Hoeber, Inc., New York City. 1934. Price, $1.50.

The Clio series of small volumes on various phases of medical history has recently had two new volumes added. The one under consideration, by the erudite professor of medical history at Düsseldorf, is a masterly presentation in small space of the achievements of German and Austrian physicians in the fields of medicine, surgery and the specialties. The amount of knowledge added by the Teutons is indeed remarkable: one need only glance at the names Paracelsus, Friedrich Hoffman, Stahl, Haller, van Swieten, Johannes Müller, Theodor Schwann, Virchow, Koch, von Behring, Ehrlich, Röntgen, Pettenkoffer, von Graefe—to mention just a few of the outstanding ones.

The growth of medicine in Germanic lands is traced from the crude beginning in the ancient times, through the middle ages and the fruitful eighteenth and nineteenth centuries down to the present much specialized age. Haberling misses the great contribution made unwittingly by Hahnemann, in that he showed us the natural history of disease uninfluenced by drugging and so eventually pointed the way to a more sane therapy. The editor of the series makes good the omission in a footnote.

This series of books which can be put in the pocket is a splendid undertaking and should do much to popularize the much neglected subject of the history of medicine, a full knowledge of which renders full of meaning the trends of medical thought as we see them today. This is a worthy companion to the preceding volumes.

J. R.

The Mother's Encyclopedia. Edited by MARY E. BUCHANAN, managing editor of *The Parents' Magazine.* Articles contributed by 130 authors. xvii + 959 pages; 4 vols., 12 × 18 cm. Home and School Book Service, The Parents' Publishing Assoc., Inc., New York City, N. Y. 1933.

This encyclopedia is unique in that it is the first time that an attempt has been made to publish in book form a series of articles covering the whole field of child care from the parent's viewpoint. The editor of this four-volume set of books has gathered articles written by some of the foremost authorities in the field of child health and training, child psychology, nutrition, sex education, family relationships,

play and play equipment. All the articles at one time appeared in *The Parents' Magazine*, but these articles have been condensed and edited wherever necessary to bring them strictly up to date. Cross references under every subject, sub-titles on nearly every page and a voluminous index in the final volume make it possible to find quickly any subject under consideration.

Of the 130 men and women who have contributed to this encyclopedia, 31 are physicians. The articles are written in a sane and scientific manner without the usual hodge-podge that is so frequently found in books on health written for the laity. There is nothing said that would lead patients to self-medication, as is the usual result of lay reading of medical articles. Physical health is fully discussed, but the largest number of pages is taken up in the discussion of child guidance and the emotional development of the individual.

At the end of the encyclopedia is a table of contents grouped by age interests: infancy, pre-school age, school age, adolescence, all ages and parenthood. Under infancy are such articles as Bathing the Baby, Weaning the Baby, Respiratory Diseases, and Fear. In the second grouping are such articles as Enuresis, Habit Training, Night Terrors, Sleep Routine, Thumbsucking, and Answering Children's Questions. In the school age group some of the articles are How to Choose the Right School, Physical Growth, Home Study, Creative Education, and Social Training. Under adolescence are such subjects as The Foods Needed, Friction in the Family, Cosmetics, Delinquency, Scouting, Nervous Breakdowns, Love, and Vocational Guidance. Some of the other titles picked at random are Budgeting the Family, Convalescent Occupations, Adoption, How Big Should a Family Be, Maternity Clothes, Eye Protection, Divorce, Dancing, Masturbation, Obedience, and Health Guidance.

Since most physicians are parents and as puzzled over the problems of bringing up children as their lay patients, the physician will find considerable help in this encyclopedia as well as a good deal of interesting reading, which will give him a better insight into the problems he is so frequently consulted about.

J. L. McC.

Klassifikation der Schizomyceten (Bakterien) Versuch einer wissenschaftlichen Klassifikation der Bakterien auf botanischer Grundlage. By PROF. DR. ERNST PRIBRAM, D.Z. Professor für Bakteriologie und Präventiv-Medizin an der Loyola University, School of Medicine, Chicago, Illinois. Paper, 143 pages. Franz Deuticke, Leipzig and Vienna. 1933.

The investigators to whom bacteriology owes its rapid development during the latter part of the last century were untrained in taxonomy and the rules of biological nomenclature. The results were quite naturally the frequent adoption of faulty names for bacteria and the lack of an adequate and satisfactory system of classification. A number of attempts have since been made to correct these errors but the suggested changes have not had official sanction. On the other hand these newer names and more recent systems have been used by some authors, while others retain the older terminology and classification. This has led inevitably to a condition bordering on chaos in the fields of nomenclature and taxonomy. Pribram now presents a new system. This monograph represents the work and experience of some 20 years and offers a classification differing materially from that suggested in 1929 by the same author. In his terminology he follows quite strictly the biological code and also leans heavily on the suggestions offered by the Committee of the Society of American Bacteriologists.

In his classification the author makes use of the work of his predecessors but has deviated from their systems in many ways. He has attempted to meet the requirements of exactness and elasticity; the latter by the use very largely of only one attribute as a characteristic of a group and by making subdivisions for each character.

This elasticity is wanting in former classifications which thus allow no place for transitional forms or for new hitherto unknown species.

The author's monograph is in two parts, preceded by a tabular synopsis of schizomycetes. The first explains this table and discusses the nomenclature and classification. The second part is devoted to the classification of the cultures of bacteria at present in the Kral collection in Vienna. There is an excellent index and an extensive bibliography.

Pribram divides the bacteria into three subclasses: algobacteria, eubacteria, and mycobacteria. The algobacteria include those forms adapted to life in water, and some of the parasitic and pathogenic microörganisms. This subclass contains organisms transitional between bacteria and algae, and others bridging the gap between the bacteria and the protozoa. The algobacteria are arranged in their various families distributed among four orders. The eubacteria include most of the "true bacteria" not placed in the first subclass; they are arranged in five families under two orders. The mycobacteria are subdivided into two orders. One of these contains the aërobic and the anaërobic, spore-bearing bacilli, each in a separate family; and the other, distributed between two families, most of the bacteria recently grouped in the order actinomycetales by Bergey and others.

In comparing the classification adopted by Pribram with some of the other modern systems we find many divergencies. Thus, whereas in the latter, the sulphur bacteria are placed in a single order, here they are distributed among several orders of the algobacteria. Again, the "slime bacteria" are generally arranged in a single family but are here placed among the algobacteria in two families. Indeed, one of the genera (Myxococcus) is found in the same family with *Vibrio cholerae* and *Ps. aëruginosa* (*B. pyocyaneus*), a rather startling juxtaposition. Also the spirochetes are put in an order of the algobacteria containing some of the sulphur bacteria, although in a different family, it is true. The cocci, which heretofore have all been classified in a single family, are found distributed among several families of algobacteria and eubacteria. Whereas most of them are classed in the first of these groups, the streptococci, including the pneumococcus, are discovered in the same order, but in a different family, of eubacteria as the proteus and acidophilus groups. The genus *Neisseria,* however, because of its strict adaptation to the animal organism, is placed in a family of the eubacteria with the brucella, the hemorrhagic septicemia, and the hemoglobinophilic groups. The classification of the spore-bearing bacteria removes them further from the other "true bacteria" and brings them into closer relationship with the tubercle bacillus, the diphtheria bacillus, and the actinomycetes than is usual. Also in the arrangement of the genera of actinomycetales in families, Pribram differs from the Committee of the Society of American Bacteriologists and from Bergey. These citations give some indication of the degree to which the classification offered in this monograph diverges from former systems. The author publishes his work in the full knowledge that it will call forth much opposition and criticism. May this discussion serve to stimulate interest in the solution of the problems and hasten the day of the adoption of a definitive system of taxonomy.

F. W. H.

COLLEGE NEWS NOTES

Acknowledgment is made of the following gifts to the College Library of publications by members:

Dr. Elliott P. Joslin (Fellow), Boston, Mass.—1 book, "Diabetic Manual."

Dr. Samuel M. Feinberg (Fellow), Chicago, Ill.—1 book, "Allergy in General Practice."

Dr. Joseph R. Darnall (Fellow), Ancon, C. Z.—2 reprints.

Dr. C. Glenville Giddings (Fellow), Atlanta, Ga.—1 reprint.

Dr. Arthur H. Jackson (Associate), Washington, Conn.—2 reprints.

Dr. Henry S. Houghton (Fellow), Chicago, Ill., has resigned as associate dean of the Division of Biological Sciences and director of the University Clinics, University of Chicago, to become advisory representative of the China Medical Board, beginning January 1, 1935. Dr. Houghton was formerly dean of the University of Iowa College of Medicine. The China Medical Board, as an agency of the Rockefeller Foundation, owns and supports the Peiping Union Medical College.

Dr. Phillipp Schonwald (Fellow), Seattle, Wash., addressed the Rocky Mountain Tuberculosis Conference, Colorado Springs, Colo., September 17 to 19, on "A Modification of the Blood Sedimentation Test in Tuberculosis."

Dr. Harold S. Davidson (Fellow), Atlantic City, N. J., has been selected as General Chairman for the annual meeting of the American Therapeutic Society, meeting in Atlantic City, June 7 to 8, 1935.

Dr. Zacharias Bercovitz (Associate), formerly of the Pyengyang Union Christian Hospital, Pyengyang, Chosen, Korea, has completed some postgraduate work at the London School of Tropical Medicine and announces he will resume practice at 889 Lexington Avenue, New York City. Dr. Bercovitz has been appointed to the clinic staff in gastro-enterology of the New York Post Graduate Medical School and Hospital.

Dr. Seale Harris, Jr. (Associate), Nashville, Tenn., has been promoted to associate professor of medicine at the Vanderbilt University School of Medicine.

Dr. Rock Sleyster (Fellow), Wauwatosa, Wis., was the recipient of the gold seal of the State Medical Society of Wisconsin at their annual dinner, September 13. Dr. Sleyster is editor of the state society's journal. He was formerly president and secretary of the society, and he is now vice-chairman of the Board of Trustees of the American Medical Association.

At the formal opening of the new headquarters for the Lilly Research Laboratories, Indianapolis, on October 11, the following Fellows of the College were speakers: Sir Frederick Banting, Toronto; Dr. Elliott P. Joslin, Boston; and Dr. George R. Minot, Boston.

Dr. David P. Barr (Fellow), Busch professor of medicine, Washington University School of Medicine, St. Louis, delivered a series of three lectures before the Honolulu County Medical Society, September 12 to 14. His titles were "The Pituitary Gland," "Hypoglycemia and Related Conditions" and "Parathyroid Gland and Calcium Metabolism."

Dr. William B. Castle (Fellow), Boston, Mass., gave the first Harvey lecture this year, October 18, at the New York Academy of Medicine, "The Etiology of Pernicious and Related Macrocytic Anemias."

The Philadelphia General Hospital, under the chairmanship of Dr. Russell S. Boles (Fellow), has inaugurated a series of Saturday morning clinics from 11 to 1 o'clock, covering a broad variety of medical and surgical subjects, with demonstration of cases, but without operative clinics. These clinics are conducted in the interests of the general practitioner and are open to the medical profession and to medical students. At the first clinics, October 6, Dr. David Riesman (Fellow), Dr. Thomas M. McMillan (Fellow) discussed "Recognition of the Failing Heart," Dr. Edward A. Strecker (Fellow) presented a clinic on "The Neuroses as Encountered by the General Practitioner." On October 13, Dr. Arthur C. Morgan (Fellow) presented a clinic on "Physical Signs of Pulmonary Tuberculosis." On October 20, Dr. Daniel J. McCarthy (Fellow) presented a clinic on "The Cerebral Apoplexies." On October 27, Dr. Robert G. Torrey (Fellow) presented a clinic on "Rheumatic Heart Disease."

Research Fellowship of the American College of Physicians

At a meeting of the Board of Regents at Chicago, Ill., April 15, 1934, the following resolution was adopted:

> "*Resolved*, that the Board of Regents establish a Fellowship in the amount of $1,800.00 to be known as the 'Research Fellowship of the American College of Physicians' and to be awarded each year on the recommendation of the Committee and the approval of the Board of Regents."

The Committee on Awards, appointed by the Board of Regents, is as follows:

David P. Barr, St. Louis, Chairman
Arthur R. Elliott, Chicago
James H. Means, Boston
William J. Kerr, San Francisco
O. H. Perry Pepper, Philadelphia

The Committee proceeded immediately after the adoption of the resolution to obtain applications for this Fellowship. The names of a number of individuals applying for similar fellowships were obtained from the National Research Council, and from other sources. After reviewing these candidates' records and communicating with each, the names of two were selected by the Committee and presented to the Board of Regents of the American College of Physicians for final selection.

Dr. Frederick Kellogg, of San Francisco, was awarded the Fellowship, and his work began on September 15. Dr. Kellogg obtained his A.B. degree at Stanford University in 1927, and his degree in medicine at Harvard University Medical School in 1931. He then worked for a period of time with Dr. Paul White, until he returned to California to take up clinical research work at the University of California Hospital. He has published a number of articles chiefly on cardiology and on anemia.

The problem Dr. Kellogg intends to follow out during the coming year on the Fellowship of the American College of Physicians is a study of hemoglobin regeneration and the relative effectiveness of various dietary factors before and after gastrectomy. This work will be done in association with Dr. Stacy R. Mettier (Fellow). Dr. Kellogg also hopes to pursue some work on phonocardiography with Dr. William J. Kerr (Fellow).

It is not too early to point out that this same Fellowship will be open again next year, and that applications may be filed at any time through the Executive Offices of the College.

Fellowship Insignia for Academic Gown

Occasional queries from manufacturers of academic gowns indicate some Fellows of the American College of Physicians are not familiar with the official method of indicating Fellowship or Mastership in academic dress.

There is no official gown for the American College of Physicians, but a special insignia to be attached to any regular or special gown a member may already have. For Fellowship, the insignia is a cross of the shape of that of the Key of the College, three inches in height, of green velvet, with the seal of the College stitched in solid gold braid, to be attached and worn on the right side of the academic gown. For Mastership, the insignia is a similar cross, except of gold cloth with green braid.

These insignia may be obtained, ready for stitching to the gown, through the Executive Offices of the College, 133–135 S. 36th St., Philadelphia, Pa.

Circulation of Annals of Internal Medicine

In compliance with the regulations of the Code Authority for the Periodical Publishing and Printing Industry (A–3), the American College of Physicians, publishers of the Annals of Internal Medicine, presents the following statement concerning the circulation of said journal for the period beginning January, 1934, and ending June, 1934:

Average gross circulation —3,197
Average net paid circulation—3,074

Subscribed and sworn to by E. R. Loveland, Executive Secretary of the American College of Physicians, this eighth day of October, 1934.

B. M. Snover,
Notary Public

My commission expires April 8, 1937
(seal)

OBITUARIES

DR. GEORGE WALTER HOLDEN

1866–1934

By the death of Dr. George Walter Holden, of Denver, from coronary thrombosis on July 11, 1934, Colorado lost one of her ablest and best known physicians. Born in Barre, Mass., September 17, 1866, his early education was obtained in the Barre Academy, and in the Mount Herman Academy at Northfield, Mass. Following a business course Dr. Holden's artistic nature craved a medical career and when he had saved enough money he entered the University of Vermont at the age of 26, graduating in medicine in 1895. After hospital experience in Boston a general practice was undertaken in North Brookfield, Mass. He was overtaken with pulmonary tuberculosis and came to Colorado where his fame was made as a specialist in that disease.

When Mr. Lawrence C. Phipps, former United States Senator from Colorado, conceived and built the Agnes Memorial Sanatorium for Tuberculosis, his family physician, Dr. Holden, was appointed Superintendent and Medical Director, which position he held from 1904 to 1932 when the institution closed. While Dr. Holden's ability as a well-trained physician was thoroughly tested in this long and faithful service, a marked administrative and disciplinarian capacity was developed which made the Agnes Memorial Sanatorium recognized as one of the best sanatoria in the country.

Dr. Holden was a member of the American Clinical and Climatological Association, the American Hospital Association, the American Sanatorium Association, the American Public Health Association, the National Tuberculosis Association (Vice-President and Director), the Colorado Tuberculosis Association (President), the Denver Tuberculosis Society (President and Director), and the Colorado Hospital Association (Vice-President). Dr. Holden was also a Fellow of the American Medical Association and of the American College of Physicians.

While not a frequent contributor to medical literature Dr. Holden was interested in the investigation of such rare conditions as aspergillosis of the lungs. Dr. Holden gave himself to such activities as the Child Research Council and possessed all the qualities of a true and earnest physician.

GERALD B. WEBB, M.D., F.A.C.P.,
Governor for Colorado.

DR. BENJAMIN GUTMANN

Dr. Benjamin Gutmann (Fellow), 144 Livingston Avenue, New Brunswick, N. J., died August 7, 1934, at the Middlesex Hospital after several months' illness from bronchiogenic carcinoma.

Dr. Gutmann was born at South Amboy, N. J., December 29, 1877. He received his preliminary education from the schools of his native town and entered the Glenwood Military Academy, Matawan, N. J., from which he graduated in 1893. He entered the Jefferson Medical College, Philadelphia, Pa., in 1893 and graduated in 1897. He returned to his native town, New Brunswick, and practiced general medicine until 1913 when he went abroad to study at Vienna and Berlin and returned again to resume his practice.

In 1919 he did special work at Harvard University Graduate School and was at the Massachusetts General Hospital, Boston, and the Presbyterian Hospital, New York City. Upon his return he limited his practice to Internal Medicine. Dr. Gutmann was Chief, Medical Service, Middlesex General Hospital, and St. Peter's General Hospital, New Brunswick, at the time of his death.

He was married to Marie Louise Fisher, daughter of Charles and Ella De Hart Fisher, November 15, 1904, and is survived by four daughters, Margaret, Elizabeth, Anne and Mrs. Willard Potter.

Dr. Gutmann was a member of the Middlesex Medical Society, the New Jersey State Medical Society, the American Medical Association and a Fellow of the American College of Physicians since 1929. He was also a member of the Rutgers Medical Club, Anglo-American Society of Berlin, American Association of Vienna and the Academy of Medicine of Northern New Jersey.

The profession and College have lost a worthy member.

CLARENCE L. ANDREWS, M.D., F.A.C.P.,
Governor for New Jersey.

DR. ISADORE D. BRONFIN

1886–1934

Born in Russia in 1886, Dr. Bronfin came to the United States in 1902. He was educated at the University of New York and graduated in medicine at the Long Island College Hospital in 1911. Developing pulmonary tuberculosis Dr. Bronfin came to Colorado in 1920 and, as so many of his predecessors had done, took up the specialty of tuberculosis in which field he became a national authority. Dr. Bronfin became Superintendent of the Jewish Consumptive Relief Society and was appointed Medical Director of the National Jewish Hospital in 1927. Absorbed in his work and indefatigable in his efforts to help the tuberculous, his own affliction relapsed and his death occurred July 30, 1934, following a series of serious pulmonary hemorrhages. Dr. Bronfin was loved and respected by all the profession of Colorado. He was a member of the faculty of the University of Colorado School of Medicine, and was a conscientious attendant of all medical society meetings. Dr. Bronfin is survived by his wife, Mrs. Elizabeth Bronfin, and by two sons.

GERALD B. WEBB, M.D., F.A.C.P.,
Governor for Colorado.

DR. CURRAN POPE

Dr. Curran Pope of Louisville, Kentucky, died September 21, 1934, at his home. He had been an Associate of the American College of Physicians since 1920. He was born in Louisville on November 12, 1866, and after graduating from public and high schools received his degree in Medicine from the University of Louisville Medical Department, 1889. He took postgraduate courses in New York, London, Paris, Vienna and Berlin, and became resident physician at the Central State Hospital in 1891. He was connected with the Hospital College of Medicine, the Louisville College of Medicine, Kentucky School of Medicine and the University of Louisville Medical Department during the years 1892 to 1910. He was very much interested in physiotherapy and, at the time of his death, was Director of the Pope Hospital in Louisville. He was a past President of the Ohio Valley Medical Association, Western Physical Therapy Association and the American College of Physical Therapy. He was the author of a book on " Practical Hydrotherapy " and several hundred articles and many editorials contributed to leading medical magazines of this country.